

**Remarks/Arguments:**

Claims 12-24, newly presented, are pending.

Claims 1-11 are canceled, without prejudice or disclaimer, with claim 11 being canceled pursuant to restriction.

Present (new) claim 12-23 contain the subject matter of claims 1-10, rewritten to address the issues raised in the rejection under §112, ¶2, discussed below and otherwise to more clearly define the instant invention. Present claim 24 provides a packaged unit of the (claim 12) blood plasma as described (at least implicitly) in the paragraph at lines 10-15 of page 4 of the instant specification; and, similarly, present “pharmaceutical composition” claim 22, which replaces claim 9, adds that the blood plasma is “in the form of transfusion unit dose.”

Claims 1-10 were rejected under 35 U.S.C. §112 as being allegedly indefinite. Reconsideration is requested.

Specifically, the PTO alleges that the recited terminology “non-Caucasian population” is indefinite. More broadly, the PTO alleges that terms such as “Caucasian” and “Non-Caucasian” fail to satisfy the requirements of §112, ¶2, citing in support the general purpose Random House Dictionary (online), which provides two definitions for “Caucasian”—one relating to races and ethnic groups and the other relating to a geographic region, i.e., the Caucasus mountains. The PTO additionally maintains that “Caucasian” and “Non-Caucasian” are not modern scientific terms, but political ones. Applicants must disagree, with all dues respect, with the PTO's finding as to the terminology at issue.

The correct test for indefinite claim language is whether one of ordinary skill in the art would be confused as to the meaning of subject matter defined by the language at issue. *In re Kroekel*, 183 USPQ 610 (CCPA 1974). Applying this test demonstrates that the language at issue satisfies the requirements of 35 USC 112, ¶2.

A person of ordinary skill in the art would readily understand the meaning of the recited "non-Caucasian population" in the context of the presently claimed invention. The language at issue constitutes well known and accepted nomenclature in the scientific/medical community. For example, the specialized dictionary MedlinePlus Medical Dictionary, available online at <http://www.nlm.nih.gov/medlineplus/mplusdictionary.html>, provides two clear definitions for "Caucasian" (online printout attached), i.e.,

- 1: of or relating to the white race of humankind as classified according to physical features
- 2: of or relating to the white race as defined by law specifically as composed of persons of European, North African, or southwest Asian ancestry

The following scientific publications (copies attached) are cited to demonstrate the actual use of "Caucasian" and "non-Caucasian" in the prior art, i.e., throughout the last 36 years.

- Owens et al.; CALIFORNIA MEDICINE 118: 33-37, May 1973
- McDonnell et al.; JOURNAL OF CLINICAL MICROBIOLOGY, Vol. 26, No. 6 June 1988, p. 1202-1206
- Sutcliffe et al.; RHEUMATOLOGY, 1999; 38: 1130-1137
- Denver et al.; DIABETES CARE, Vol. 26, No. 8, August 2003, 2256-2260
- Moltich et al.; J Am Soc Nephrol 14: S103-S107, 2003

- Venkat et al.; Int J Emerg Med (2008) 1:287-296

This list represents a very small selection of numerous other publications.

Consequently the claim term "non-Caucasian population" covers the ethnic group complementary to the Caucasian ethnic group.

The PTO suggests using concentration of markers to characterize plasma used as raw material. Unfortunately, to applicants' knowledge there do not exist markers to characterize plasma in an adequate form. It is known that blood group distribution (types A, B, AB, and O) differs between ethnic groups but according to applicants' research, in connection with developing the presently claimed invention, there also have to be differences in antibody concentration. These differences are only noticeable on a statistical basis as titers of individuals scatter significantly. Use of the teachings of the invention as described and claimed in the present application depends on the origin (location of donation center and known distribution of local ethnic groups) of blood/plasma donations.

The PTO states that the titer of the antibodies in the donated blood, not the ethnical background of the donors, is critical for the quality of the resulting product. Applicants do agree that an accurate determination of iso-agglutinin titers and volume of each plasma/blood donation would allow the determination of an optimum mixture. But, this approach would effect an unacceptable and unmanageable workload and costs, by boosting the consumption of test kits and quality reducing storage of thawed plasma/blood until the optimum mixture is calculated. This

handicap is eliminated with ease by the knowledge of the statistical, ethnical composition of donors, as indicated above.

There is also consent about the assessment of subject-matter related to virus inactivation and claimed forms of plasma, *i.e.*, frozen, lyophilized, liquid, and dried, as these matters as such are already known and also indicated in the description.

With regard to rejected claim 10, proper process-claim language is recited in the claim, *i.e.*, the step of "repeated large volume plasma exchange." Even if considered insufficiently precise, the language at issue still satisfies the requirements for patentable subject matter under §101.

Some latitude in the manner of expression and the aptness of terms should be permitted even though the claim language is not as precise as the examiner might desire. Examiners are encouraged to suggest claim language to applicants to improve the clarity or precision of the language used, but should not reject claims or insist on their own preferences if other modes of expression selected by applicants satisfy the statutory requirement.

MPEP 2173.02. Moreover, rejected claim 10 is one of the claims in the elected Group I invention (*i.e.*, the claims of invention Group I of the restriction requirement, of record). Accordingly, claim 10 was entitled to examination on the merits, even if considered indefinite. MPEP 2173.02.

Present claim 23 contains the "treatment" subject matter of rejected claim 10 and merely adds the word "comprising"—to recite "'comprising repeated large volume plasma exchange" (emphasis added). Since claim 10 satisfies the requirements for patentable subject matter under §101, present (new) claim 23—containing subject matter found in claim 10—satisfies the requirements for patentable subject matter under §101 and, as such, is entitled to examination on the merits.

In view of the foregoing amendments and remarks, the rejection of claims under §112, ¶2, is overcome. Withdrawal of the rejection appears to be in order.

Claims 1-3, 6-10 are rejected under 35 U.S.C. §103(a) as being unpatentable over WO 99/07390 in view of Aubert. Claims 4-6 are rejected under 35 U.S.C. §103(a) as being unpatentable over WO 99/07390 in view of Aubert and in further view of US 2003/0133829. Reconsideration of the rejections is requested.

To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 180 USPQ 580 (CCPA 1974). "All words in a claim must be considered in judging the patentability of that claim against the prior art," *In re Wilson*, 165 USPQ 494, 496 (CCPA 1970), "and it is error to ignore specific limitations distinguishing over the [prior art] reference." *Ex parte Murphy*, 217 USPQ 479, 481 (PO Bd. App. 1982). A "ground of rejection is simply inadequate on its face . . . [when] the cited references do not support each limitation of [the] claim." *In re Thrift*, 63 USPQ2d 2002, 2008 (Fed. Cir. 2002). When the claimed invention requires modification of the prior art, there is no obviousness under §103 when "[t]he prior art does not suggest . . . [the] modification . . . or provide any reason or motivation to make the modification." *In re Laskowski*, 10 USPQ2d 1397, 1398 (Fed. Cir. 1989).

The present (and rejected) claims provide a "blood plasma" obtained from pools of donated blood, limited to at least "10%" of the donors being from "a non-Caucasian population." With respect to this limitation the statement of rejection argues (Office Action, page 7):

Whether the plasma is obtained from populations which are termed “non-Caucasian” or not is of little patentable weight particularly since the term is ambiguous. It is the titer of the antibodies in the plasma which is critical not the skin color of the human from which it is derived.

With all due respect, the aforesaid arguments are not well taken.

First of all, as explained above with evidentiary support (*i.e.*, the attached documents cited in the explanation) the “non-Caucasian population” recited in the present claims is not ambiguous; but, on the contrary, the claim terminology satisfies the requirements of §112, ¶2.

Secondly, whether the PTO considers “the titer of the antibodies in the plasma . . . is critical [and] not the skin color of the human from which it is derived” is of no moment. It is applicants' sole prerogative to define the claims. *In re Pilkington*, 162 USPQ 145, 148 (CCPA 1969).

Accordingly, finding the language at issue “of little patentable weight fails to follow the proper standards for analysis of the claims §103(a). To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *Royka, supra*. “All words in a claim must be considered in judging the patentability of that claim against the prior art.” *Wilson*, 165 USPQ at 496.

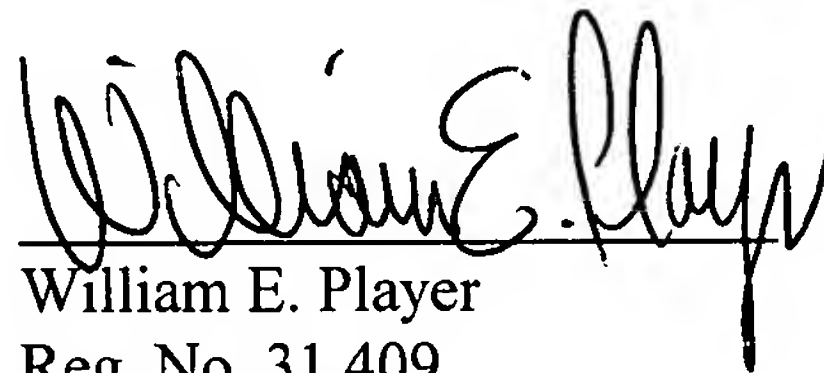
Nothing in the cited references, taken alone or in combination, teaches or suggests the limitation on the present claims to “donors” of “a non-Caucasian population”. In fact, the statement of rejection does not allege that such a teaching or suggestion is found in the cited reference. Accordingly, since the “cited referenced does not support each limitation of [the rejected] claim[s],” the rejection is “inadequate on its face. *Thrift* 63 USPQ 2d @2008. Since the cited references fail

to “provide any reason or motivation” to modify the teachings of the cited references to use “a non-Caucasian population” of blood donors as recited in the present claims, there is no obviousness under §103. *Laskowski* 10 USPQ 2d@1398.

In view of the foregoing amendments and remarks, the instant rejections of claims under §103(a) are overcome. Withdrawal of the rejections appears to be in order.

Favorable action is requested.

Respectfully submitted,

A handwritten signature in black ink, appearing to read "William E. Player", is written over a horizontal line.

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## Medical Dictionary

One entry found for Caucasian.

Main Entry: **Cau·ca·sian**

Pronunciation: 'kō-'kā-zhən, -'kazh-ən

Function: *adjective*

1 : of or relating to the white race of humankind as classified according to physical features

2 : of or relating to the white race as defined by law specifically as composed of persons of European, North African, or southwest Asian ancestry

- **Caucasian** *noun*

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### Pronunciation Key

\ a \ as a in abut	\ g \ as g in go	\ r \ as r in red
\ 'a iə \ as u in abut	\ h \ as h in hat	\ s \ as s in less>
\ ə \ as e in kitten	\ i \ as i in hit	\ sh \ as sh in shy
\ ər \ as ur/er in further	\ ī \ as i in ice	\ t \ as t in tie
\ a \ as a in ash	\ j \ as j in job	\ th \ as th in thin
\ ā \ as a in ace	\ k \ as k in kin	\ th \ as th in the
\ ä \ as o in mop	\ k \ as ch in ich dien	\ ū \ as oo in loot
\ aũ \ as ou in out	\ l \ as l in lily	\ ŭ \ as oo in foot
\ b \ as in baby	\ m \ as m in murmur	\ v \ as v in vivid
\ ch \ as ch in chin	\ n \ as n in own	\ w \ as w in away
\ d \ as d in did	\ ŋ \ as ng in sing	\ y \ as y in yet
\ e \ as e in bet	\ ō \ as o in go	\ yū \ as you in youth
\ 'ē iē \ as ea in easy	\ ɔ \ as aw in law	\ yū \ as u in curable
\ ē \ as y in easy	\ ɔi \ as oy in boy	\ z \ as z in zone
\ f \ as f in fifty	\ p \ as p in pepper	\ zh \ as si in vision

## Relationship of Health-Related Variables to Levels of Anti-Polyribosylribitol Phosphate Antibodies in Adults

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To identify adults who may be at risk for *Haemophilus influenzae* type b disease by virtue of low levels of antibody against the *H. influenzae* b capsule and who may thus benefit from receiving *H. influenzae* b vaccine, we correlated serum anticapsular antibody levels of 388 adult patients with 26 health-related variables, including 3 personal characteristics, 10 laboratory values, 4 drug use categories, and 8 disease categories. Steroid use was consistently associated with low levels of anticapsular antibody; associations were also found between low antibody levels and both non-Caucasian race and increasing age. However, less than 4% of the antibody variability could be attributed to these factors, and they were not predictive of low antibody levels. Thus, although *H. influenzae* b infections are seen in adults with predisposing medical conditions, on the basis of the present findings, use of the *H. influenzae* b vaccine in adults cannot be recommended.

*Haemophilus influenzae* is a common inhabitant of the human respiratory tract and exists either in an encapsulated form, in which the organisms possess one of six serotypes of polysaccharide capsule (types a to f), or in a nonencapsulated form (nontypable). Nontypable *H. influenzae* may cause local respiratory infections, such as otitis media, sinusitis, and bronchitis, but rarely causes invasive infections in immunologically normal persons (6).

Invasive infections with type b strains occur more frequently than with nontypable strains or type a, c, d, e, and f strains (8, 11, 16); in children, *H. influenzae* type b is a major cause of serious infections, such as meningitis, septic arthritis, cellulitis, and epiglottitis. In adults, although serious infections with *H. influenzae* type b are uncommon, several clinical studies have suggested that certain groups of adults, such as the elderly and those with diabetes, malignancies, alcoholism, immunodeficiencies, and other debilitating illnesses (3, 14, 20, 22), may be predisposed to invasive *H. influenzae* b infections.

Susceptibility to systemic *H. influenzae* b infections in children is strongly associated with absence of serum antibodies directed against the type b capsular polysaccharide, polyribosylribitol phosphate (PRP) (12). Similarly, immunization of children more than 2 years old with purified type b capsular PRP vaccine, which has recently been marketed in the United States for children 24 months of age, confers protection against invasive disease (13). In contrast, the relationship between anticapsular antibodies and protection against invasive *H. influenzae* b disease in adults is less well understood. In this study, to identify groups of adults that may benefit from immunization with *H. influenzae* b vaccine, we attempted to identify associations between certain underlying illnesses or health-related variables and low levels of anticapsular antibodies. Sera from 400 patients hospitalized at an adult general hospital were tested for anti-PRP antibodies, and the results were correlated with 26 health-related variables, including 3 personal characteristics, 10 laboratory values, 4 drug use categories, and 8 disease categories.

### MATERIALS AND METHODS

**Patient information.** Sera were obtained from 400 patients admitted consecutively to the University of Michigan Hospital in March 1985. The following admission information was obtained: age, sex, race, leukocyte count, granulocyte count, lymphocyte count, hemoglobin, total serum protein, total serum bilirubin, serum albumin, serum creatinine, serum glutamic oxalacetic transaminase, and serum alkaline phosphatase. The hospital records of the patients were also reviewed for evidence of underlying diseases, ethanol use, tobacco use, and immunosuppressive drug use.

**Anti-PRP antibody assay.** Serum immunoglobulin G antibodies to *H. influenzae* b capsular PRP were quantitated by using an enzyme-linked immunosorbent assay. Capsular PRP was isolated and purified from the supernatant of a broth culture of *H. influenzae* b by using the method of Kuo et al. (10), and the amount of PRP in the purified preparation was quantitated by latex agglutination, with PRP purified by Lederle Laboratories (kindly provided by Christine Williams) as a reference standard. The PRP was conjugated to tyramine (PRP-tyramine) by using cyanogen bromide as described by Anthony et al. (1) to enhance uniform binding to polystyrene microtiter plates. The PRP-tyramine was diluted in carbonate-coating buffer (21) to a concentration of 5.72 µg of PRP per ml, and U-bottom, rigid, polystyrene microtiter wells (Dynatech Laboratories, Inc., Alexandria, Va.) were coated with 100 µl (0.57 µg) of PRP-tyramine for 18 h at 4°C. Results of preliminary experiments confirmed that the microtiter wells were saturated with this amount of antigen.

After being coated, the wells were washed for 1 h with 100 µl of phosphate-buffered saline (pH 7.4) containing 0.3% Tween 20 (PBS-T). All washes and incubations were performed at room temperature on a rotating platform at 50 rpm. A total of 100 µl of each test serum, diluted 1:50 in PBS-T, was added to the wells, incubated for 1 h, and then washed twice with PBS-T for 5 min. Then, 100 µl of affinity-purified goat anti-human immunoglobulin G, heavy and light chain specific, conjugated with horseradish peroxidase (Cappel Laboratories, Malvern, Pa.) was added. After 1 h of incubation, the wells were again washed with PBS-T twice for 5 min. Next, 100 µl of substrate (34 mg of

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*o*-phenylenediamine [Sigma Chemical Co., St. Louis, Mo.] in 100  $\mu$ l of 0.1 M citrate phosphate buffer [pH 5.01] [13] with 10  $\mu$ l of 30%  $H_2O_2$  was placed into each well. The reaction was allowed to proceed for 15 min in the dark and was then terminated by adding 50  $\mu$ l of 4 N  $H_2SO_4$ . The optical density (OD) values of the contents of the wells were measured immediately on a Titertek Multiskan spectrophotometer (Flow Laboratories, Rockville, Md.) at 492 nm.

A positive control serum standard (containing 70.4  $\mu$ g of PRP-binding antibody per ml and obtained from the Office of Biologics Research and Review of the U.S. Food and Drug Administration) and two negative control serum samples (obtained from a patient with agammaglobulinemia and a 9-month-old child) were included on each microtiter plate along with the study samples. A values of the positive control serum at dilutions of 1:50, 1:250, 1:1,000, and 1:2,500 served as an internal control on each plate, generating a straight line ( $r = 0.99$ ) when graphed against the log dilution factor. The negative control sera showed no decrease in *A* with dilution. Each control and test serum specimen was diluted 1:50 in PBS-T and tested in duplicate. Anti-PRP antibody values from the study samples were expressed as normalized enzyme-linked immunosorbent assay units (EU), calculated as follows: [(OD of the test sample - OD of the negative control serum)/(OD of the positive control serum - OD of the negative control serum)]  $\times$  1,000. This formula converted the OD value of the test sample to a value in EU on a normalized scale, with the positive control standard having a value of 1,000 EU and the negative control serum having a value of 0 EU. Those serum samples with absorbance values less than that of the negative control were given a value of 0 EU. Positive values were defined as those greater than 3 standard deviations above the normalized mean values of the negative control sera. This calculated cut-off value was 44 EU. To determine the variability of the values, we tested three negative control sera on 24 wells.

**Statistical analysis.** All statistical analyses were performed by using the Michigan Interactive Data Analysis System and BioMedical Data Programs (BMDP) statistical software. Differences between the anti-PRP levels of patients with various health-related variables were tested by analysis of variance. Associations between these variables were sought by contingency table analysis for discrete variables and by all-possible-subsets regression analysis for continuous variables. For further analyses by two-way contingency table analysis, the continuous anti-PRP variables were transformed into discrete variables by coding each antibody result as detectable (greater than 3 standard deviations above the mean values of the negative control sera) or nondetectable.

Preliminary analysis revealed that the square root transformation of the dependent variable, the anti-PRP level, resulted in a closer approximation to a normal distribution among study samples. The transformed mean anti-PRP level was obtained by averaging the transformed (square root) data and then squaring the mean to return it to the original scale.

Multiple regression analysis was used to relate normalized anti-PRP values to dummy variables (which are categorical variables that have been transformed into sets of dichotomous variables) to generate potential regression models. A stepwise algorithm was also used to include all potentially significant variables in the regression model.

## RESULTS

From the 400 patients in the study, we were able to compare serum antibody levels and clinical parameters of

TABLE 1. Relationship of age and anti-PRP level in adults

Age (yr)	<i>n</i>	Mean anti-PRP level (95% confidence interval) <sup>a</sup>
<20	8	94 (0-204)
20-29	50	83 (43-123)
30-39	49	88 (46-130)
40-49	51	49 (35-63)
50-59	79	64 (39-39)
60-69	87	58 (42-76)
$\geq 70$	57	52 (38-66)
Total	381	65 (55-75)

<sup>a</sup> Expressed as EU.

388 individuals, of whom 58% were women and 42% were men. The average age of the patients was 51 years, with a range of 10 to 84 years; 86% were Caucasian, 12% were Negroid, and 2% were of other racial groups. The transformed mean-normalized anti-PRP antibody value was 40.5 EU, with a range of 0 to 850 and a median of 40 EU; the mean of the untransformed anti-PRP value was 65 EU. A total of 55% of the patients did not have detectable levels of anti-PRP antibody (values below 44 EU).

We found no correlation between any of the laboratory variables tested and anti-PRP levels. Table 1 presents the mean anti-PRP levels by patient age, grouped by decades. The correlation between the lower anti-PRP value and increasing age was 0.0934 ( $P = 0.068$ ).

Table 2 presents the mean anti-PRP levels by sex and race. By two-way contingency table analysis, the  $P$  value for the association between anti-PRP level and race (Caucasian versus non-Caucasian) was 0.051. Sex was not associated with anti-PRP level.

Table 3 presents the mean anti-PRP levels of patients for various illness variables and strata; we identified no significant associations among anti-PRP levels and any of these variables.

Table 4 presents mean anti-PRP levels in patients with four drug use variables. Steroid therapy was associated with low anti-PRP levels by analysis of variance ( $P = 0.041$ ) and by two-way contingency table analysis (Fisher exact test;  $P = 0.057$ ). Additional analysis of variance, using the collapsed variables, drug usage, and no drug usage, confirmed a significant association between low anti-PRP levels and steroid usage ( $P = 0.012$ ). We also demonstrated by analysis of variance a significant association between low anti-PRP levels and use of immunosuppressive therapy ( $P = 0.045$ ).

Least squares regression modeling with dummy variables against the transformed anti-PRP value resulted in marginally significant coefficients for steroid therapy ( $P = 0.041$ ,  $R^2 = 0.021$ ), age ( $P = 0.074$ ,  $R^2 = 0.008$ ), and steroid therapy

TABLE 2. Distribution of patients and mean anti-PRP levels for demographic variables and strata

Variable	Stratum	<i>n</i> (%)	Mean anti-PRP level (95% confidence interval) <sup>a</sup>
Sex	Male	161 (42)	44.9 (33.7-56.1)
	Female	223 (58)	36.9 (29.3-44.5)
Race	Caucasian	264 (86)	42.6 (29.0-56.2)
	Negroid	36 (12)	27.9 (7.6-48.2)
	Other	6 (2)	36.7 (0-83.3)

<sup>a</sup> Mean of transformed anti-PRP values, expressed as EU.

TABLE 3. Distribution of patients and their mean anti-PRP levels for illness variables and strata

Illness variable	Stratum	n (%)	Mean anti-PRP level (95% confidence interval) <sup>a</sup>
Diabetes mellitus	None	344 (89)	40.6 (29.2–52.0)
	<10 yr	27 (7)	47.1 (17.1–77.1)
	10–20 yr	13 (3)	21.0 (0–44.2)
	>20 yr	2 (1)	7.8 (0–38.8)
	Insulin dependent	2 (1)	69.6 (12.6–126.6)
Malignancy	None	275 (71)	42.4 (30.3–54.4)
	Low grade <sup>b</sup>	19 (5)	48.6 (0–102.5)
	Nonmetastatic	36 (9)	42.8 (0–86.1)
	Metastatic <sup>c</sup>	36 (9)	26.3 (5.8–46.8)
	Hematologic	6 (2)	2.7 (0–14.2)
Rheumatologic disease	None	345 (89)	40.9 (29.5–52.3)
	NSAIA controlled <sup>d</sup>	19 (1)	41.8 (7.2–76.4)
	Remittive agent controlled <sup>e</sup>	2 (1)	9.2 (0–46.3)
	Steroid controlled	8 (2)	51.3 (0–109.4)
	Cytotoxic agents	5 (1)	3.9 (0–32.1)
	Gout	5 (1)	30.8 (0–71.7)
	Other	4 (1)	58.10 (0–151.2)
Cardiovascular disease	None	246 (64)	40.5 (25.9–65.1)
	Hypertension only	57 (15)	36.8 (20.2–53.4)
	CAD unconfirmed <sup>f</sup>	13 (3)	62.5 (47.3–67.7)
	CAD confirmed	52 (13)	40.3 (15.7–64.9)
	Other	20 (5)	33.3 (12.2–54.4)
Pulmonary disease	None	351 (91)	39.4 (29.0–49.8)
	Minor COPD <sup>g</sup>	19 (5)	73.3 (0–156.3)
	Major COPD <sup>h</sup>	6 (2)	74.6 (0–184.7)
	>100 pack-yr	11 (3)	13.0 (0–32.2)
	Cystic fibrosis	1 (0)	47.0
Renal disease	None	375 (97)	39.8 (29.3–50.3)
	Creatinine, 2–4 U	6 (2)	26.6 (11.5–41.7)
	Creatinine, >4 U	1 (0)	205.0
	Dialysis	6 (2)	65.8 (0–196.6)
Neurologic disease	None	368 (96)	39.3 (28.9–49.7)
	Mild CVA, can do ADL <sup>i</sup>	4 (1)	18.2 (0–49.3)
	Mental retardation	1 (0)	97.0
	Seizure	6 (2)	88.5 (0–260.9)
	Quadra- or paraplegia	3 (1)	77.8 (0–343.0)
	Other	3 (1)	47.0 (0–127.4)
Liver disease	None	374 (96)	40.3 (29.5–51.0)
	Acute	3 (1)	16.5 (0–37.9)
	Minor chronic disease	9 (2)	21.1
	Major chronic disease	2 (1)	225.9 (0–452.5)

<sup>a</sup> Mean of transformed anti-PRP value, expressed as EU.<sup>b</sup> For example, prostate or skin cancer.<sup>c</sup> Head, neck, ovarian, and small cell cancers.<sup>d</sup> NSAIA, Nonsteroidal antiinflammatory agents.<sup>e</sup> Penicillamine, gold, Plaquinal controlled.<sup>f</sup> CAD, Coronary artery disease.<sup>g</sup> COPD, Chronic obstructive pulmonary disease, minimal or greater than 60 years of smoking history.<sup>h</sup> With frequent hospitalization, steroid use.<sup>i</sup> CVA, Cerebral vascular accident; ADL, activities of daily living.

and age together ( $P = 0.021$ ,  $R^2 = 0.035$ ). All-possible-subsets analysis generated a best model of age, steroid therapy, and rheumatologic illness against the transformed anti-PRP value ( $P = 0.004$ ), but the  $R^2$  value remained low, (0.038).

The assay variability (expressed as a coefficient of variation) of anti-PRP values was 4.2% for well-to-well differences, 4.1 to 32.9% for plate-to-plate differences, and 15.4% for day-to-day differences.

## DISCUSSION

Although *H. influenzae* type b is a major cause of serious infections in infants and young children, this organism rarely causes serious illness in individuals more than 4 years of age or in adults. Susceptibility to *H. influenzae* type b in young children has been associated with the absence of serum antibodies directed against capsular PRP. Natural antibodies directed against PRP develop during early childhood, and

TABLE 4. Distribution of patients and mean anti-PRP levels for drug use variables and strata

Drug use variable	Stratum	n (%)	Mean anti-PRP level (95% confidence interval) <sup>a</sup>
Alcohol use	None	195 (50)	40.3 (26.5–54.1)
	Moderate ( $\leq 3$ /day)	138 (36)	42.9 (25.9–59.9)
	Heavy ( $\geq 4$ /day)	32 (8)	30.7 (2.4–59.0)
	Unknown	23 (6)	36.6 (0–118.8)
Tobacco use	None	194 (50)	38.3 (24.4–52.2)
	1–24 pack-yr	71 (18)	42.7 (18.4–67.0)
	25–50 pack-yr	65 (17)	39.1 (11.0–67.1)
	>50 pack-yr	40 (10)	53.8 (13.3–94.3)
	Unknown	18 (5)	28.2 (8.7–47.7)
Steroid therapy	None	358 (92)	42.6 (31.5–53.7)
	<30 mg/day <sup>b</sup>	16 (4)	10.6 (0–31.0)
	>30 mg/day	10 (3)	35.1 (0–83.9)
	Previous treatment	4 (1)	10.1 (0–34.1)
Immunosuppressive therapy	None	335 (86)	42.8 (31.0–54.6)
	Any, including radiotherapy	53 (14)	25.4 (11.8–39.0)

<sup>a</sup> Mean of transformed anti-PRP value, expressed as EU.<sup>b</sup> Prednisone equivalence.

most individuals more than 4 years of age appear to be protected against invasive disease with this organism (12).

In many reports in the literature, the *H. influenzae* strains from adult patients were not serotyped (19), so the epidemiology of *H. influenzae* type b infections in adults remains unclear. In spite of this, the few reports that include adequate serotyping of *H. influenzae* isolates from adults demonstrate that type b organisms occasionally cause pneumonia with bacteremia (4) as well as other invasive infections, including cellulitis, septic arthritis, pericarditis, and epiglottitis (4, 20).

We attempted to identify certain underlying illnesses or clinical parameters in adult individuals that may be predictive of low levels of serum antibody directed against *H. influenzae* type b PRP. The only factor that was consistently identified as having an association with low serum anti-PRP levels was steroid use. However, we did not identify a relationship between the steroid dose and the level of anti-PRP antibodies. Interestingly, among patients with rheumatologic disease, those that required cytotoxic agents or remittive agents had low levels of anti-PRP antibody, whereas those that were steroid controlled did not; however, the numbers of patients in these groups are small.

Although the correlation between age and concentration of anti-PRP antibody was not statistically significant at the 5% level, a possible trend toward decreased anti-PRP antibody with increased age was observed. However, in spite of these associations, none of the variables tested were predictive of low levels of antibodies directed against anti-PRP antibody. By multivariate analysis, only 4% of the variability of the antibody levels was accounted for by the best model, indicating that many factors that we did not identify influence anti-PRP levels.

A possible explanation for our failure to identify more clinical parameters that were associated with anti-PRP levels may be that, although the total number of patients studied was large, the numbers of patients with each category and stratum tended to be small and the levels of serum anti-PRP antibody were widely variable among the patients tested. Because of this high variability, a higher number of patients within each disease category would be required to identify a significant association. In addition, identification of associa-

tions by using contingency table analysis may have been limited by our definition of antibody positive, which was any value greater than or equal to 3 standard deviations above the mean of the negative control sera. Thus, some values that we designated as negative may have been, in fact, low positive.

Previously published studies of anti-PRP levels and of responses to vaccination with the *H. influenzae* b capsular polysaccharide have used radioantigen-binding assays for antibody determination (7, 12). By this technique, the amount of antibody required to assure protection against disease in children following vaccination has been estimated to be greater than 1  $\mu$ g/ml (9). More recently, Edwards et al. (5) have demonstrated that tests of sera in different laboratories using different antigen preparations and different radioantigen-binding assay techniques resulted in widely variable results. Because of this observation and probable differences in the binding abilities of various types of antibodies, we feel that assigning a quantitative value of antibody to our test specimens based on the Office of Biologics Research and Review standard may be misleading. Thus, we have chosen to express our results in terms of EU.

Identification of a group of patients with an underlying illness predictive of low levels of anti-PRP antibody may provide a target group of adults to receive the *H. influenzae* type b vaccine. However, other factors in the immune response to PRP that are not addressed in this study, such as booster response to antigenic stimulation, may be important in protection against *H. influenzae* b infection (7). In addition, the only group that we identified as being associated with lower anti-PRP levels were those patients using steroids or immunosuppressive agents, who may be unable to generate an adequate immune response to vaccination (15, 17, 18). Furthermore, the efficacy of another polysaccharide vaccine, the pneumococcal polysaccharide vaccine, in adults remains controversial (2, 19). Thus, additional information on the susceptibility of adults to *H. influenzae* type b infection and on their responses to vaccination is necessary before *H. influenzae* b vaccine use in adults can be recommended.

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# The Diabetes Prevention Program and Its Global Implications

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**Abstract.** Type 2 diabetes affects over 150 million adults worldwide and this figure is expected to double over the next 25 yr. This increase will be accompanied by a marked increase in the number of patients with ESRD due to diabetes. We hypothesized that a lifestyle-intervention program or the administration of metformin would prevent or delay the development of diabetes. We randomly assigned 3234 nondiabetic persons with elevated fasting and post-load plasma glucose concentrations to placebo, metformin (850 mg twice daily), or a lifestyle-modification program with the goals of at least a 7% weight loss and at least 150 min of physical activity per week. The mean age of the participants was 51 yr, and the mean body mass index was 34.0 kg/m<sup>2</sup>; 68% were women, and 45% were members of non-Caucasian racial/ethnic groups. The average follow-up was 2.8 yr. The incidence of diabetes was

11.0, 7.8, and 4.8 cases per 100 person-years in the placebo, metformin, and lifestyle groups, respectively. The lifestyle intervention reduced the incidence of diabetes by 58% (95% CI: 48 to 66%) and metformin by 31% (95% CI: 17 to 43%), compared with placebo; the lifestyle intervention was significantly more effective than metformin. In conclusion, lifestyle changes and treatment with metformin both reduced the incidence of diabetes in persons at high risk and the lifestyle intervention was more effective than metformin. Because the lifestyle changes worked equally in all racial/ethnic groups in the Diabetes Prevention Program, they should be applicable to high-risk populations worldwide and may be able to reduce the projected progressive rise in the incidence of diabetes and the expected increase in ESRD.

Type 2 diabetes mellitus is a serious disease affecting approximately 4.0% of adults in the world in 1995 (1) and this prevalence has been projected to rise to 5.4% by 2025 (2). This increase is occurring to a disproportionate extent in the developing countries, especially those of Asia (2,3). The worldwide increase in the prevalence of diabetes has been accompanied by a three- to fourfold increase in the incidence of ESRD, making diabetes the single leading cause of ESRD in most countries (4). Although treatment of diabetes can prevent some complications (5,6), it does not usually restore normoglycemia or eliminate nephropathy and the other long-term complications of diabetes. Prevention of diabetes is clearly preferable (7,8).

Obesity adds to the inherent insulin resistance of type 2 diabetes, as does lack of exercise (reviewed in 9), leading to the concept that weight loss and increased activity levels may be effective in preventing diabetes in susceptible individuals. A

number of observational studies have shown that the development of diabetes is associated with increasing weight and weight gain, and is reduced with exercise (10,11), supporting this concept.

The Diabetes Prevention Program (DPP) Research Group conducted a large, prospective, randomized clinical trial involving adults in the United States who were at high risk for the development of type 2 diabetes (12,13). The study was designed to answer the following question: Does a lifestyle intervention or treatment with metformin prevent or delay the onset of diabetes?

## Materials and Methods

Twenty-seven centers participated in the DPP. The methods have been described in detail elsewhere (12). Eligibility criteria included age  $\geq 25$  yr, body mass index of  $\geq 24$  kg/m<sup>2</sup> or higher ( $\geq 22$  in Asians), and a fasting plasma glucose concentration of 95 to 125 mg/dl (5.3 to 6.9 mmol/L) ( $\leq 125$  mg/dl in the American Indian clinics) and 140 to 199 mg/dl (7.8 to 11.0 mmol/L) 2 h after a 75-g oral glucose load, *i.e.*, impaired glucose tolerance (IGT) with elevated fasting glucose levels.

Participants were randomly assigned to one of three interventions: metformin 850 mg twice daily, placebo twice daily, or an intensive program of lifestyle modification. The study initially included a fourth intervention, troglitazone, which was discontinued in 1998 because of the drug's potential liver toxicity (12,13). In the intensive lifestyle arm, the goals were to achieve and maintain a weight reduction of at least 7% of initial body weight through a healthy low-calorie, low-fat

The members of the Diabetes Prevention Program Research Group are listed in reference 13.

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diet and to engage in physical activity of moderate intensity, such as brisk walking, for at least 150 min/wk. A curriculum covering diet, exercise, and behavior modification was taught in both one-to-one and group sessions (12).

The primary outcome was the development of diabetes, diagnosed on the basis of an annual oral glucose-tolerance test (OGTT) or a semiannual fasting plasma glucose test, according to the 1997 criteria of the American Diabetes Association: fasting plasma glucose  $\geq 126$  mg/dl (7.0 mmol/L) or  $\geq 200$  mg/dl (11.1 mmol/L) 2 h after a 75-g oral glucose load (14). The diagnosis required confirmation by a second OGTT within 6 wk (12).

Assignments to metformin and placebo were double-blinded. The study design and analysis followed the intention-to-treat principle. The blinded treatment phase was terminated 1 yr early, in May 2001, on the basis of data obtained through March 31, 2001, the closing date for this report. Details of the statistical analyses used have been reported previously (13).

## Results

Between 1996 and 1999, 3234 study participants were randomly assigned to one of the three interventions (1082 to placebo, 1073 to metformin, and 1079 to the intensive lifestyle intervention). The three groups had similar baseline characteristics, including all measured risk factors for diabetes (15). The mean duration of follow-up was 2.8 yr (range, 1.8 to 4.6).

The goal of weight loss of  $\geq 7\%$  was achieved by 50% of the participants in the lifestyle-intervention group by the end of the core curriculum (at 24 wk), and 38% had a weight loss of at least 7% at the time of the most recent visit. The percentage of subjects in the lifestyle-intervention group who met the weekly goal of at least 150 min of physical activity was 74% at 24 wk and 58% at the most recent visit. Dietary change was assessed only at 1 yr. Daily energy intake decreased by a mean ( $\pm$  SEM) of  $249 \pm 27$  kcal in the placebo group,  $296 \pm 23$  kcal in the metformin group, and  $450 \pm 26$  kcal in the lifestyle-intervention group ( $P < 0.001$ ). Average fat intake, which was 34.1% of total calories at baseline, decreased by  $0.8 \pm 0.2\%$  in the placebo and metformin groups and by  $6.6 \pm 0.2\%$  in the lifestyle-intervention group ( $P < 0.001$ ). The percentage of participants who took at least 80% of the prescribed dose of the study medication was slightly higher in the placebo group than in the metformin group (77% versus 72%,  $P < 0.001$ ). Ninety-seven percent of the participants taking placebo and 84% of those taking metformin were given the full dose of one tablet (850 mg in the case of metformin) twice a day; the remainder were given one tablet a day to limit side-effects.

Changes in weight and leisure physical activity in all three groups are shown in Figure 1. Participants in the lifestyle intervention cohort had much greater weight loss and a greater increase in leisure physical activity than did participants in the metformin or placebo cohorts. The average weight loss was 0.1, 2.1, and 5.6 kg in the placebo, metformin, and lifestyle-intervention groups, respectively ( $P < 0.001$ ).

The cumulative incidence of diabetes was significantly lower in the metformin and lifestyle-intervention groups than in the placebo group throughout the follow-up period (Figure 2), the crude incidence rates being 11.0, 7.8, and 4.8 cases per

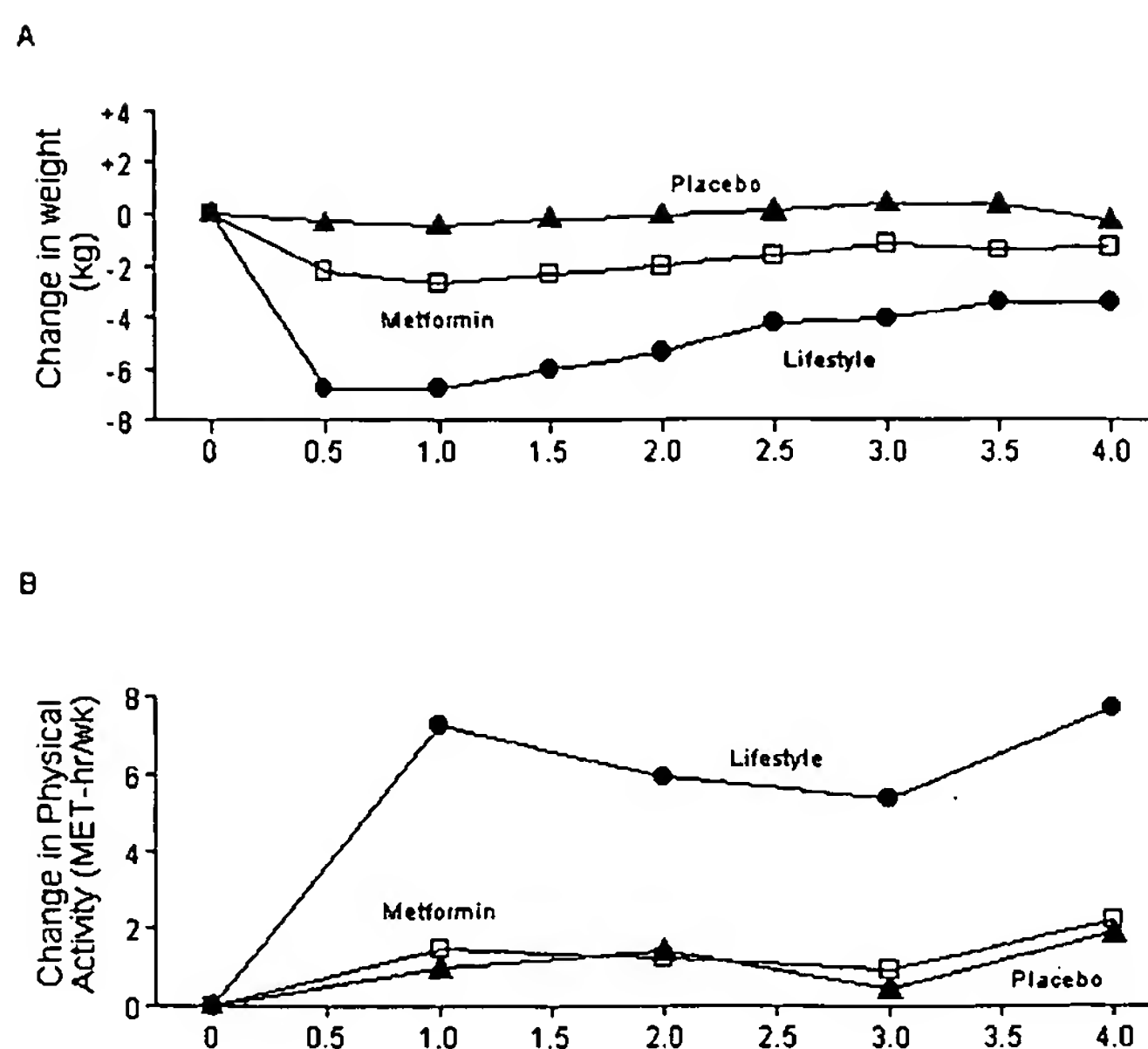


Figure 1. Changes in (A) body weight and (B) leisure physical activity according to study group. Each data point represents the mean value for all participants examined at that time. The number of participants decreased over time because of the variable length of time that persons were in the study. For example, data on weight were available for 3085 persons at 0.5 yr, 3064 at 1 yr, 2887 at 2 yr, and 1510 at 3 yr. Changes in weight and leisure physical activity over time differed significantly among the treatment groups ( $P < 0.001$  for each comparison).

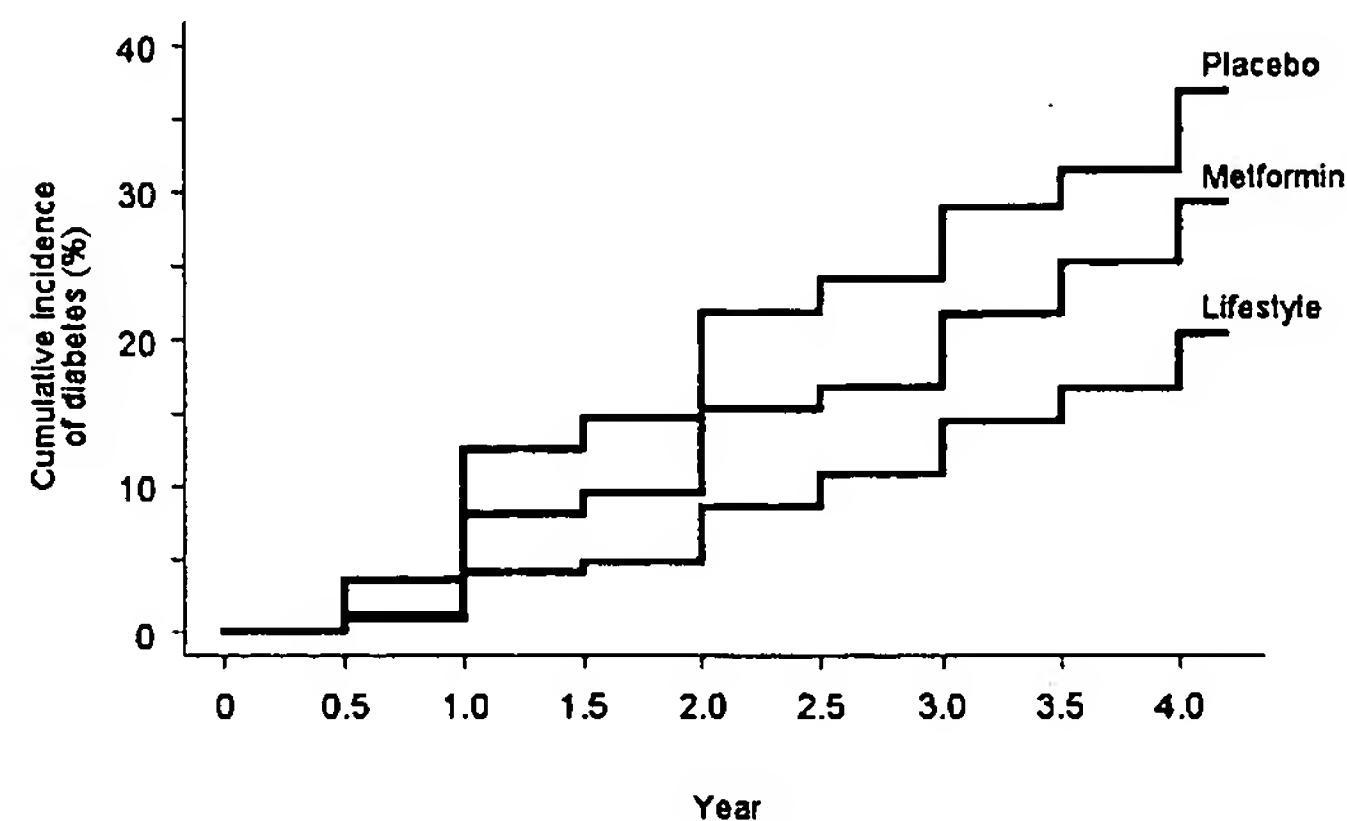


Figure 2. Cumulative incidence of diabetes according to study group. The incidence of diabetes differed significantly among the three groups ( $P < 0.001$  for each comparison).

100 person-years for the placebo, metformin, and lifestyle-intervention groups, respectively. The incidence of diabetes was 58% lower (95% CI: 48 to 66%) in the lifestyle-intervention group and 31% lower (95% CI: 17 to 43%) in the metformin group than in the placebo group. The results of all three pairwise group comparisons were statistically significant by

the group-sequential log-rank test. None of these results were substantially affected by adjustment for baseline characteristics. The estimated cumulative incidence of diabetes at 3 yr was 28.9%, 21.7%, and 14.4% in the placebo, metformin, and lifestyle-intervention groups, respectively. On the basis of these rates, the estimated number of persons who would need to be treated for 3 yr to prevent one case of diabetes during this period is 6.9 (95% CI: 5.4 to 9.5) for the lifestyle intervention and 13.9 (95% CI: 8.7 to 33.9) for metformin.

Treatment effects did not differ significantly according either to gender or to race or ethnic group. The lifestyle intervention was highly effective in all subgroups. The effect of metformin was less with a lower body mass index ( $<30 \text{ kg/m}^2$ ) and age over 60 yr. Thus, the advantage of the lifestyle intervention over metformin was greater in older persons or those with a lower body mass index than in younger persons or those with a higher body mass index.

The rate of gastrointestinal symptoms was highest in the metformin group, and the rate of musculoskeletal symptoms was highest in the lifestyle-intervention group. Hospitalization and mortality rates were unrelated to treatment. No deaths were attributed to the study interventions.

## Discussion

The results from this study show that diabetes can be prevented or delayed in a substantial proportion of those at high risk for the disease (13). The incidence of diabetes was reduced by 58% with the lifestyle intervention and by 31% with metformin, compared with placebo. These effects were similar in men and women, and in all racial and ethnic groups. The intensive lifestyle intervention was as effective in older participants as it was in younger participants. The risk reduction we found with lifestyle intervention was the same as that found in a similar study conducted in Finland (16), and was higher than the reductions associated with diet (31%), exercise (46%), and diet plus exercise (42%) in a study in China (17). Our study, however, was not designed to test the separate contributions of dietary changes, increased physical activity, and weight loss on the reduction in the risk of diabetes.

The incidence of diabetes in the placebo group (11.0 cases per 100 person-years) was higher than anticipated (12) and higher than seen in observational studies (10). The incidence rates of diabetes were similar among racial and ethnic groups despite differences in these subgroups in observational population-based studies (1,10). Racial- and ethnic-group differences in the incidence of diabetes were presumably reduced in our study by the selection of persons who were overweight, and had elevated fasting and postload glucose concentrations—three of the strongest risk factors for diabetes.

Drugs used to treat diabetes had not previously been shown to be effective for its prevention, perhaps because of small sample size and other methodological differences (7). However, in this study, metformin was effective, although less so than the lifestyle intervention. Metformin was less effective in persons with a lower baseline body mass index or a lower fasting plasma glucose concentration than in those with higher

values for these variables. These findings are consistent with the observation that metformin suppresses endogenous glucose production, the main determinant of fasting plasma glucose concentrations (9).

In the United States the prevalence of IGT is modestly greater than that for diabetes (diagnosed and undiagnosed) (15.6% *versus* 12.3%), according to data from the Third National Health and Nutrition Examination Survey (1). If this is extrapolated to the entire world, where it is estimated that in the year 2000 there were approximately 155 million people with diabetes, the prevalence of IGT can be estimated to have been 197 million people (2). Furthermore, with the estimated projection of the prevalence of diabetes in the year 2025 of 300 million people (2), it can be estimated that 380 million people will have IGT. In areas of Asia and other previously underdeveloped areas, it is thought that this increasing prevalence of glucose intolerance is reflective of improvements in nutrition, hygiene, control of infectious diseases, and overall access to better medical care with increases in life expectancy along with decreased exercise associated with urbanization (2,3).

The fact that the benefits of weight loss and exercise were effective across all racial/ethnic groups, including African Americans and Asian Americans, in the DPP has important implications for the world population for diabetes in general and diabetic nephropathy in particular. The incidence of patients with diabetic ESRD increased approximately threefold between the 1980s and 1990s in various countries around the world (4). Where the two types of diabetes have been studied separately, it has been found that the total numbers with type 1 diabetes with ESRD have remained relatively constant but that there has been an extraordinary increase in the number of patients with type 2 diabetes with ESRD (4). At present, in most programs caring for patients with ESRD around the world, there are more patients with type 2 diabetes than those with type 1 (4).

The increasing number of patients with type 2 diabetes having nephropathy worldwide is, in part, related to the fact that those of non-Caucasian racial origin with type 2 diabetes have higher risks for diabetic nephropathy. It is known from studies in the United States and other countries that blacks, Asians, Latinos, and Native Americans have increased risks for development of diabetic nephropathy (18,19) and that this is not due solely to differential access to health care. For example, in a recent study of patients receiving relatively uniform clinical care in a managed care program in California, the adjusted hazard ratios for the development of nephropathy, compared with Caucasians, were 2.03, 1.85, and 1.45 for blacks, Asians, and Latinos, respectively (20). However, most of the increase is due to the rapid increase in the number of individuals developing diabetes along with their overall improvement in longevity (4).

Once diabetes develops, glycemic control and BP control are important means of delaying and possibly preventing the development and progression of nephropathy (5,6,21,22). Subsequently, angiotensin converting enzyme inhibitors and angiotensin II receptor blockers appear to have selective further

benefit in decreasing the rate of progression of established nephropathy (23). Although these aspects of care for more advanced stages of disease are thought to be cost effective (24,25), it clearly would be advantageous to prevent the disease altogether, or delay it as long as possible.

If the modest lifestyle interventions of 5 to 7% weight loss and increased activity of 150 min/wk shown to be effective in the DPP and other studies (15,16) were implemented in all susceptible populations, there would be a substantial reduction in the incidence of diabetes worldwide. The fact that the DPP interventions were equally effective across all racial/ethnic groups suggests that this approach to prevention of diabetes would be expected to ultimately reduce both the prevalence of diabetes and the prevalence of ESRD due to diabetes. Community-based programs that could be instituted at low cost to increase physical activity and help in weight loss have been advocated in this regard by the American Diabetes Association and the National Institutes of Health (8). Ultimately, the benefits would depend on whether glucose concentrations could be maintained at levels below those that are diagnostic of diabetes and whether the maintenance of these lower levels improve long-term outcomes. In addition, weight loss and exercise may also have independent effects in reducing cardiovascular disease (26).

In summary, the DPP showed that treatment with metformin and modification of lifestyle were two highly effective means of delaying or preventing type 2 diabetes. The lifestyle intervention was particularly effective, with one case of diabetes prevented per seven persons treated for 3 yr. Thus, it should also be possible to delay or prevent the development of diabetic nephropathy and other complications, substantially reducing the individual and public health burden of diabetes. A longer-term follow-up study of the DPP cohort is currently underway to help answer these questions.

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# Congenital Hypertrophic Pyloric Stenosis

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*In a large metropolitan general hospital, a high incidence of congenital hypertrophic pyloric stenosis was noted in non-Caucasian groups. Bile-free emesis was consistently reported, and admission was frequently delayed. A prompt diagnosis following admission was not always possible. Unequivocal palpation of a right upper quadrant mass was successful in less than half of the patients in this series, and radiographic studies were helpful in establishing the proper diagnosis in the remainder. Liver fracture can occur with improper abdominal palpation techniques.*

*Despite a surprisingly high complication rate, the ultimate result of operative therapy is uniformly excellent. Three patients not operated upon who were followed for more than two years still have evidence of gastric dysfunction. Postoperative emesis following adequate operation is not unusual, occurring approximately one-third of the time. When postoperative emesis is protracted, incomplete pyloromyotomy should be considered.*

CONGENITAL HYPERTROPHIC PYLORIC STENOSIS holds a special place in the practice of surgery because of its frequent incidence, "classical" findings, and excellent cure rate following the Ramstedt operation.<sup>1-6</sup>

The purpose of this paper is to review an experience with 50 consecutive cases of this entity

treated during an eight-year period (1963-1970) in a large metropolitan general hospital, and to compare and contrast some of our findings with respect to the incidence, diagnosis, and complications with the findings in series reported in the literature from pediatric surgical centers.

## Clinical Material

The 50 infants, 39 boys and 11 girls, whose cases are here reviewed were seen at the Sacramento Medical Center, a large metropolitan general hospital with heavy experience in trauma and acute disease. Thirty-eight of the infants were of

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Caucasian background, the remainder equally divided between the Afro-American and Latin-American races. Only eight were first-born males, and four were first-born females. Ten of the infants had a sibling with the same disease entity. Three were premature, the remainder full-term.

### Clinical Presentation

*History.* A well-defined symptom complex has uniformly been reported.<sup>7-10</sup> The single most consistent presenting symptom was bile-free emesis, which was present in all cases. Projectile vomiting, however, was described in only 20 infants. Constipation and failure to thrive were both presenting complaints in this group. The average duration of symptoms was about ten days, with the shortest period two days and the longest 21. The average age at onset was four and a half weeks, with the youngest two weeks of age, and the oldest eight weeks.

*Examination.* Physical findings have historically been of prime importance in establishing a preoperative diagnosis.<sup>7-10</sup> Visible peristaltic waves passing from left to right in the upper abdomen were noted in only 17 of the 50 infants in the present series. A firm spherical tumor mass was noted on palpation of the abdomen (confirmed by at least two examiners) in 24 of the infants. An equivocal finding of a mass in the right upper quadrant, necessitating a radiological contrast study for diagnostic confirmation, occurred in 18 cases. In seven of the infants, a tumor mass was not palpable, but the diagnosis was made by subsequent upper gastrointestinal series. In one instance, the correct diagnosis was established only by postmortem examination.

The state of hydration on admission was recorded as mild, moderate, or severe, depending upon body weight, skin turgor, and urinary output. On this basis, 34 infants were described as mildly dehydrated, eight as moderately so, and an additional eight as severely dehydrated.

*Laboratory Studies.* The carbon dioxide content of the blood, which tends to provide prognostic information regarding an infant's ability to withstand a general anesthetic,<sup>2,4,5,11</sup> was recorded in all 50 cases. In 31 cases it was reported normal (24 to 28 mEq per liter), in ten moderately alkalotic (28 to 32 mEq) and in eight severely alkalotic (greater than 32 mEq). In one case the carbon dioxide content on admission was 10 mEq per liter.

The association of hyperbilirubinemia and congenital hypertrophic pyloric stenosis has been reported and discussed without a substantiated cause for this apparent relationship.<sup>2,12,13</sup> Six of the 50 patients presented with hyperbilirubinemia ranging from 2.1 mg to 9.7 mg per 100 ml. The bilirubin elevations in five of the six cases primarily represented the indirect-reacting fraction.

### Treatment

A Ramstedt pyloromyotomy was performed in 46 of the 50 cases. General inhalation anesthesia was used in 44 cases, local infiltration anesthesia in two. Delays before operation averaged 2.4 days; the longest delay was ten days. This time included time for diagnostic confirmation and preoperative fluid and electrolyte replacement therapy.

Four patients were treated non-operatively by a regimen utilizing intravenous fluid and electrolyte infusion, alternating nasogastric lavage and gavage, and graded feedings. There was one death in this group, that of an infant who presented with a three-week history of bile-free emesis, a carbon dioxide content of 10 mEq per liter, and severe dehydration. A diagnosis could not be established on physical examination. Death occurred on the second hospital day despite aggressive attempts to correct the fluid and electrolyte imbalance. The remaining three patients not surgically treated required hospital stays of 12, 14, and 15 days. They have been followed for a minimum of two years, and each has intermittent symptoms of gastric dysfunction, poor feeding habits, intermittent episodes of nausea and vomiting, and retarded growth and development.

### Results

The long-term results in all the 46 patients' cases were excellent, despite a postoperative complication rate of 26 percent (Table 1). There were eight complications not directly related to the intraoperative procedure, comprising seven cases of bacterial pneumonitis and one of aspiration pneu-

TABLE 1.—Postoperative Complications in a Series of 46 Cases

Right lower lobe pneumonitis .....	7
Aspiration pneumonitis .....	1
Wound infection .....	3
Incomplete pyloromyotomy .....	1
<b>TOTAL .....</b>	<b>12</b>

monitis. There were three minor wound infections. In one case, the pyloromyotomy was incomplete, and reoperation was necessitated on the third post-operative day.

Intraoperative duodenal perforation occurred in 18 instances (39 percent), but in all instances the lesion was recognized at the time of operation and the duodenal opening was suitably closed. In two instances, a fracture-hematoma of the anterior margin of the right lobe of the liver was found at laparotomy. This was probably related to the frequency of preoperative physical examinations and overenthusiasm or frustration on the part of an examiner.

### Postoperative Management

Oral intake was begun four to six hours after operation unless there had been duodenal perforation. The feeding regimen was generally uniform, and consisted of increasing hourly increments of glucose solution for four to six hours. If this was well tolerated, quarter-strength to half-strength formula feedings were begun. In cases complicated by intraoperative duodenal perforation, a small nasogastric tube was connected to dependent drainage for 24 hours, and the feeding regimen was then begun following removal of the tube. There were 14 instances (30 percent) of postoperative emesis of more than one feeding.

The average postoperative hospital stay was 4.5 days.

### Associated Congenital Anomalies

There were nine infants (18 percent) with associated congenital anomalies, which included bilateral inguinal hernias (3), interventricular septal defects (3), patent ductus arteriosus (1), cryptorchidism (1), and microglossia (1).

### Discussion

Several pertinent points relating to the diagnosis and treatment of congenital hypertrophic pyloric stenosis need reemphasis on the basis of the cases represented by this experience. The 4:1 ratio of males to females is quite typical, but the non-Caucasian incidence of 24 percent is not.<sup>2,7</sup> The average age at onset of symptoms has been reported as three weeks, and the duration of symptoms before treatment as one to nine weeks.<sup>5,8,14</sup> In this series, the average age at onset was 4.5 weeks, and the average duration of symptoms 1.5

weeks. Bile-free emesis, a constant presenting symptom in cases reported in the literature,<sup>2,5-10,14</sup> was present in all cases in our series.

The need for appropriate preoperative replacement therapy to correct dehydration and electrolyte imbalance is well recognized as an important prerequisite to the attainment of satisfactory operative risk.<sup>2,4,5,11</sup> The fact that there were no operative deaths in this series reflects, in part, adequate intravenous replacement therapy before operation.

Hyperbilirubinemia has been reported as an occasional finding with congenital hypertrophic pyloric stenosis. No apparent causal relationship exists with this association, but the coincidence was noted in six cases in our series—a higher incidence than previously noted in the medical literature.<sup>2,12,13</sup>

Non-operative treatment of this condition has some proponents (primarily in the European medical community), but results are generally disappointing.<sup>10,15-18</sup> Four of the patients in this series were treated non-operatively. Because of extreme dehydration and acidosis, one infant died on the second hospital day, never having attained suitable operative-risk status. The remaining three required prolonged stay in hospital and detailed nursing care. All three have persistent gastric dysfunction and have failed to thrive.

Often when an infant comes to a teaching institution with a presumptive diagnosis of congenital hypertrophic pyloric stenosis, he may be examined by more than the usual number of trainees. Despite admonitions to the housestaff on the inherent dangers of vigorous digital abdominal examination in an irritable infant with a tense abdominal wall, two patients early in this series were found to have fracture hematomas of the anterior margin of the right lobe of the liver at the time of laparotomy. Since this complication has been recognized, irritable infants with tense abdomens are examined during oral feeding and concomitant nasogastric decompression.<sup>19</sup>

Reviewing and evaluating a series of this type occasionally leads to a challenge of preconceived ideas. It has been often stated that this disease frequently involved the first-born male in a family, but in this study the incidence of first-born males was only 16 percent. We therefore support the conclusion of Delprat and Pflueger that pyloric stenosis is not a "disease of the first-born."<sup>20</sup> It has also been stated that one's diagnostic acumen is deficient when an infant presents with a "classical" history for this disorder, and a right upper-



Figure 1.—Radiographic confirmation of congenital hypertrophic pyloric stenosis—"string and shoulder" sign.

quadrant abdominal mass cannot be palpated. A mass was palpated in fewer than half the cases in the present series. Fortunately, the addition of an x-ray contrast study to help confirm or exclude the diagnosis is well tolerated and easily done.<sup>21-23</sup> The diagnosis is confirmed radiographically by the finding of either a "string-and-shoulder sign," or a "doubletrack sign" (Figures 1 and 2). There were no false-positive diagnoses in this series.

### Technical Considerations

The genesis of a curative operative procedure for this pathological entity occupies a special place in the history of surgery. Until 1907, gastroenterostomy was commonly used in the treatment of this condition, but the operation often carried a mortality rate of 50 percent or more.<sup>8-10</sup>

Fredet, in 1907, introduced longitudinal pyloromyotomy with transverse approximation of the pylorus.<sup>10</sup> In 1912, Ramstedt used longitudinal pyloromyotomy alone, and the operation which bears his name has withstood the test of time.<sup>2,5,6,10,14</sup>

Many types of abdominal surgical incisions have been recommended, and each has its proponents.<sup>24</sup> Historically, however, the various abdominal wall incisions recommended were developed in an effort to minimize wound dehiscence and evisceration, which carried a high mortality in debilitated infants who did not have the benefit of modern preoperative fluid and electrolyte replacement therapy. These recommended incisions cover the spectrum from right paramedian muscle-retracting incisions, to subcostal muscle-splitting

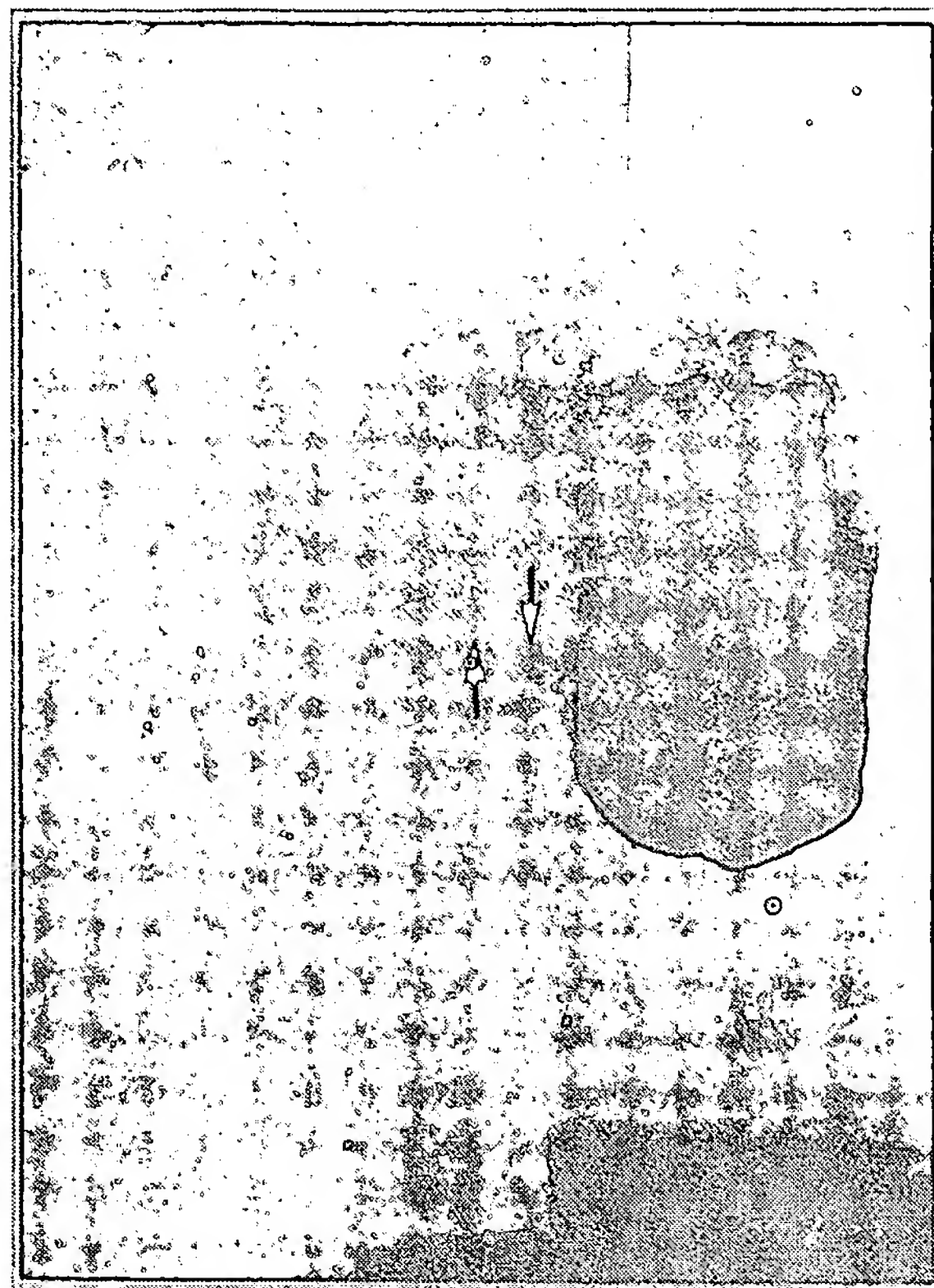


Figure 2.—Radiographic confirmation of congenital hypertrophic pyloric stenosis—"doubletrack" sign.

incisions, to transverse incisions with rectus transection, and finally, to transverse skin incisions with rectus retraction or rectus splitting. In the well-prepared infant, the abdominal incision essentially becomes one of cosmetic consideration only.

Right paramedian incision was used in 18 of the 46 operative cases in this series, subcostal with muscle splitting in nine, transverse with rectus transection in 11 and transverse with rectus splitting in eight. All three wound infections occurred in the latter group. In no case did dehiscence occur.

Potential morbidity and mortality secondary to the Ramstedt procedure are primarily related to an unrecognized duodenal perforation or an incomplete pyloromyotomy, although the latter complication is infrequently reported.<sup>2,4,5,7-9,16</sup> In no single operative procedure in the surgeon's armamentarium is the admonition "Stay out of the duodenum!" more appreciated and earlier learned than in treating one's first case of congenital hypertrophic pyloric stenosis. Despite this level of awareness, duodenal perforation occurred in 18 of the 46 operative cases in the present series. An

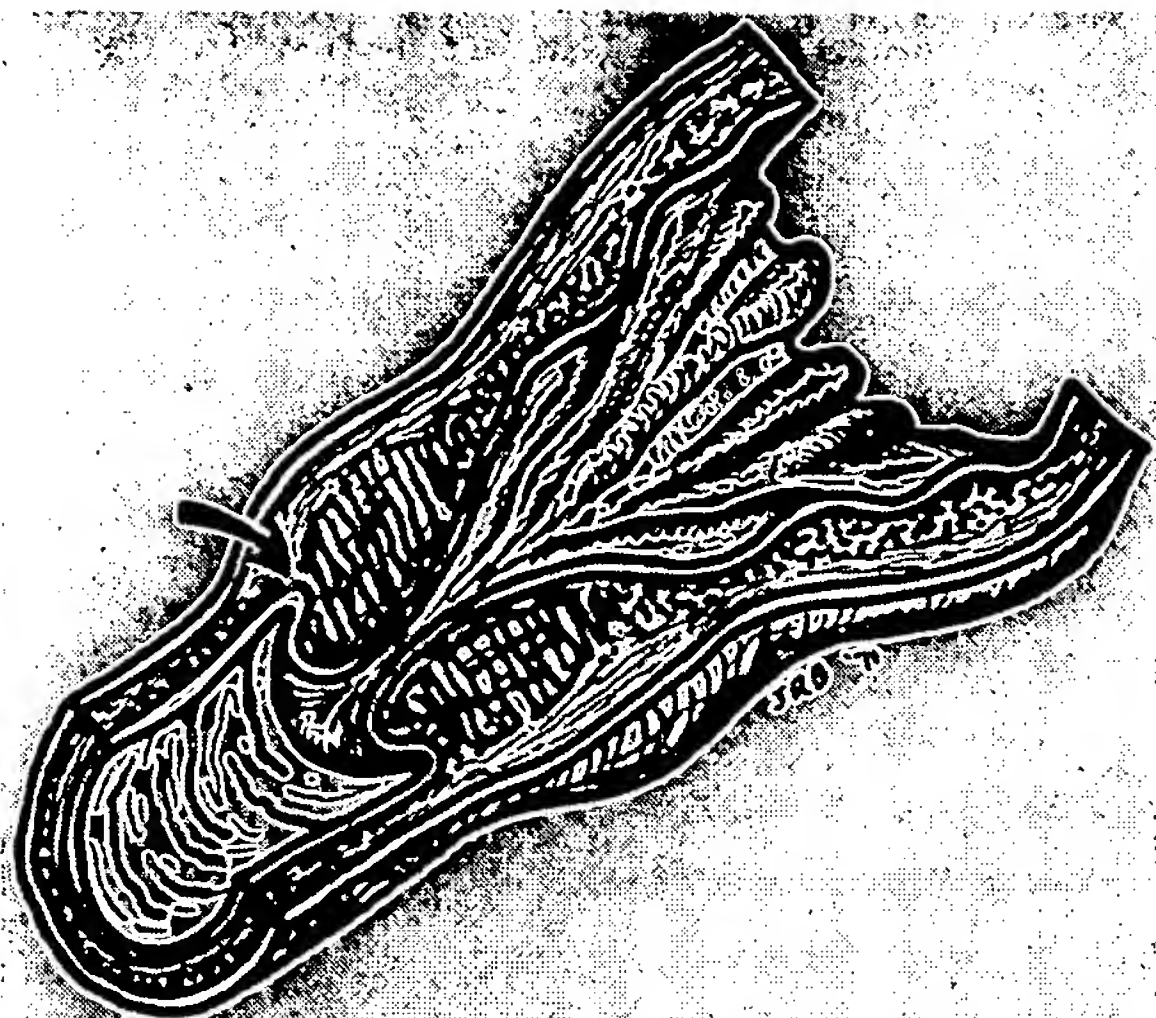


Figure 3.—Longitudinal section of pylorus demonstrating hypertrophied circular muscle and the duodenal "fornix."

appreciation of the anatomy of the hypertrophied pylorus and the duodenal "fornix" (arrow, Figure 3) is necessary for the correct performance of the Ramstedt procedure.

A longitudinal incision on the anterosuperior pylorus is carried several millimeters proximally and distally beyond the gross extent of the hypertrophied pylorus to allow the normal seromuscular layers at the antral and duodenal ends to "give" when the pyloric musculature is divided. The hypertrophied circular muscle is gently split throughout its length until the pyloric mucosa bulges to the level of the serosa. By gentle compression of the antrum, a leak at the duodenal end is made readily apparent. Occasionally, it will be necessary to suture-ligate a small bleeding vessel at the proximal or distal end of the pyloromyotomy.

### Complications

Postoperative emesis after the initiation of oral intake generally does not imply a continued obstruction at the pylorus.<sup>2,3,6</sup> It may, however, reflect a hurried postoperative feeding schedule.<sup>25</sup> Fourteen of the 46 patients who were surgically

treated had transient postoperative emesis (more than two episodes) in the early feeding period. In only one instance was postoperative emesis protracted, and in that case a subsequent gastrointestinal contrast study revealed an incomplete pyloromyotomy. Re-operation was carried out the third postoperative day without sequelae.

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# The association of socio-economic status, race, psychosocial factors and outcome in patients with systemic lupus erythematosus

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## Abstract

**Objective.** To determine the relationship between socio-economic status, race, psychosocial factors and outcome in patients with systemic lupus erythematosus (SLE).

**Methods.** One hundred and ninety-five patients with SLE were studied at two centres in the UK (London and Birmingham). Information about sociodemographics, income, employment status, social support and satisfaction with care was obtained. Outcomes were assessed by end-organ damage, disease activity and employment status.

**Results.** Non-Caucasian race, longer disease duration, higher disease activity and lower level of education were associated with more organ damage in SLE. More satisfaction with access to care and interpersonal aspects of care, but less satisfaction with time spent with doctors, were also associated with more damage. Very long disease duration was associated with higher disease activity. Patients with higher disease activity, lower level of education and from the Birmingham centre were more likely not to be working due to their lupus.

**Conclusion.** Race and socio-economic status, as well as clinical and psychosocial factors, determine outcome in SLE.

**KEY WORDS:** SLE, Socio-economic status, Race, Psychosocial factors, Organ damage, Disease activity.

The survival of patients with systemic lupus erythematosus (SLE) has improved over the last 40 yr from an estimated 5 yr survival of 50% to >90%. The 10 yr survival rate is now nearly 90% [1]. As a consequence, outcome measures other than death are necessary to assess prognosis. It is generally agreed that the prognosis of patients with SLE should be described by three domains: quality of life, disease activity and accumulated damage [2].

We have previously determined the predictors of quality of life in patients with SLE [3]. Several indices have been developed to assess disease activity in SLE. Of these, the Systemic Lupus Activity Measure (SLAM), the British Isles Lupus Assessment Group (BILAG) and the Systemic Lupus Erythematosus Disease Activity

Index (SLEDAI) have been the most widely used, and have been shown to be valid and reliable [4]. Morbidity in patients with SLE also relates to damage produced in individual organs either as a result of previous inflammation or as a complication of therapy [5]. For this reason, a damage index was developed and validated by members of the Systemic Lupus International Collaborative Clinics (SLICC) [6].

Several disease-related and general demographic characteristics such as gender, race, age at onset, socio-economic status and psychosocial factors have been examined as possible factors affecting prognosis in SLE with somewhat controversial results [7]. Although race has been shown to be important in the development and prognosis of SLE, it has been difficult to separate the effects of race from socio-economic status. Most of the studies that have evaluated this relationship were performed in the USA which has a primarily private health care system. The UK has a primarily publicly funded health care system and, in theory, all patients should

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have equal access to care, irrespective of income. We therefore felt that it was timely to conduct a study in the UK examining the relationship between socioeconomic status, race, psychosocial factors and outcome in patients with SLE. We have assessed the outcome as determined by the SLAM activity, the SLICC damage indices and the employment status in 195 consecutive patients with SLE attending two specialist lupus clinics in London and Birmingham.

## Methods

A prospective, cross-sectional study of 195 consecutive patients with SLE attending two specialist lupus clinics in the UK was undertaken (107 patients from the Centre for Rheumatology/Bloomsbury Rheumatology Unit, University College London and 88 from the Rheumatology Department of Birmingham University). These patients were also enrolled in a trinational study of health services utilization and outcomes in SLE [8]. Patients from London were assessed between June and September 1995. Patients from Birmingham were assessed between January and April 1996. Both units used the same protocol. Sociodemographic data including age, sex, race, marital status and educational level expressed as years of education were obtained. Disease duration (calculated from the time patients first fulfilled the revised ACR criteria for the classification of SLE [9]), disease activity [assessed by the revised SLAM (SLAM-R)], and individual and total end-organ damage scores [using the SLICC/American College of Rheumatology Damage Index (SLICC/ACR DI)] were also determined during the same clinic visit. Patients also filled in self-report questionnaires about their social support (Interpersonal Support Evaluation List; ISEL), satisfaction with care (Patient Satisfaction Questionnaire; PSQ), income and employment status (economic questionnaire) [10].

## Measures

SLAM was developed by Liang and colleagues in Boston, based on the consensus of members of the Lupus Council of the American College of Rheumatology. It includes 32 items, divided into 11 organ systems, and assigns a degree of severity on a scale of 1–3 with 1 being mild and 3 most severe. The total possible score is 86 [11]. It has been shown to be comparable to other commonly used disease activity indexes including the BILAG and SLEDAI [12]. Its validity and reliability have been shown previously [4, 12]. We have used the revised SLAM (SLAM-R) in this study, which differs very little from the original SLAM [4].

The SLICC/ACR DI is a measurement of cumulative end-organ damage in SLE. It was introduced in 1992. Its validity and reliability have been shown previously [6, 13–15]. Damage is described as non-reversible change, not related to active inflammation, occurring since the onset of lupus, ascertained by clinical assessment and present for at least 6 months unless otherwise

stated. It is defined for 12 organs or systems: ocular (range 0–2), neuropsychiatric (0–6), renal (0–3), pulmonary (0–5), cardiovascular (0–6), peripheral vascular (0–5), gastrointestinal (0–6), musculoskeletal (0–6), skin (0–3), gonadal (0–1), endocrine damage (0–1) and malignancy (0–2). The maximum possible total score is 46.

Social support was considered as a psychosocial factor which may determine disease outcomes. Social support is a process by which interpersonal relationships promote psychological well-being and protect people from health declines, particularly when they are facing stressful life circumstances. It enables recipients to use effective coping strategies by helping them come to a better understanding of the problem faced, increasing motivation to take instrumental action, and reducing emotional stress, which may impede other coping efforts. In addition, support may encourage the performance of positive health behaviours, thus preventing or minimizing illness and symptom reporting [16]. The ISEL scale has been used to assess social support [17]. It includes scales measuring four social support functions: Belonging (availability of people one can do things with); Appraisal (availability of someone to talk to); Tangible (availability of material aid); Self Esteem (availability of a positive comparison when comparing oneself with others). Each ISEL subscale consists of 10 items with four possible responses (0–3), with a total subscale score range from 0 (least support) to 30 (most support). The total ISEL score is the sum of the four component scores (0–120). This questionnaire has been used previously in a study of patients with SLE in Canada and was shown to correlate with direct and indirect costs of disease, which are another aspect of outcome [10].

We felt that patients' degree of satisfaction with medical care they receive may also be an important psychosocial factor influencing disease outcomes. Patient satisfaction rating is a personal evaluation of health care services and providers. It is intentionally subjective. The Medical Outcomes Study Patient Satisfaction Questionnaire was originally developed by Ware *et al.* in the USA [18]. We have used Version IV in this study. This questionnaire enquires about global level of satisfaction, considering all health care providers and settings, without specifying a particular provider or hospitalization. It is comprised of seven dimensions, including general satisfaction, technical competence (i.e. diagnosis and management), interpersonal satisfaction (e.g. courtesy and respect), communication satisfaction, time spent with doctor and access to care. The financial dimension was omitted because it poses questions of limited applicability in the British system of health care funding. Each scale is scored between 0 and 100. Higher scores indicate more satisfaction with care. A summary score has not been developed. This questionnaire was chosen because there are no specific patient satisfaction questionnaires developed for UK patients and, of the validated patient satisfaction questionnaires developed in the USA, this was most appropriate for UK patients with the minor modification mentioned above.

### Statistical analysis

The analyses were based on ordinal logistic regression models [19]. In such models, there is an ordered outcome variable,  $Y$ , which has, say,  $K$  categories. Thus,  $Y$  can take the values 1, 2, ...,  $K$ . Associated with each study subject are explanatory variables  $X_1, X_2, \dots, X_p$  which code information about the subject. The relationship between the explanatory variables and  $Y$  is specified as:  $\log(\text{probability}(Y > j)/\text{probability}(Y \leq j)) = A_j + B_1.X_1 + B_2.X_2 + \dots + B_p.X_p$ . The regression coefficients, the  $B_i$  values, correspond to the log odds ratio. Thus,  $\exp(B_i)$  represents, for all values of  $j$ , the change in the odds of  $Y$  being bigger than  $j$  vs being less than or equal to  $j$ , when the explanatory variable  $X_i$  is increased by one unit. For example, if  $B_i = 0.69$  corresponding to a variable coded 0 for Caucasian patients and 1 for non-Caucasians, then the model indicates that the odds of being in a higher damage category for non-Caucasians are twice (i.e.  $e^{0.69} = 2$ ) those of a Caucasian patient.

The ordered outcomes were a grouped version of the SLICC damage scores with six categories (see Table 1) and a grouped version of the SLAM scores in three categories (0–4, 5–10, >10). We have also considered employment status as another outcome measure. The outcome variable, not working due to lupus, was a binary classification (not working due to lupus vs working or not working due to other reasons). The explanatory variables were considered in three groups. The first group corresponding to clinical centre, ethnic origin and disease duration (coded as three levels: <10, 10–20, >20 yr) were viewed as baseline variables and were entered first into the model for purposes of adjustment. Their inclusion was not based on any significance tests. Age was not included because of its strong correlation with disease duration. Since the association between damage and disease duration was stronger than that of damage and age, disease duration was included in the models.

The second group of explanatory variables corresponding to three socio-economic variables (education level, the ISEL scores and marital status) were first entered singly into an ordinal regression model including the baseline variables and then entered jointly to examine their influence after adjusting for other socio-economic variables. The last group comprises the six dimensions of the PSQ. They were added singly and jointly to the model that included both the baseline variables and the

three socio-economic variables. Two of the socio-economic variables, years of education and the ISEL scores, have both a natural ordering and a large range. To avoid undue influence being given to a few extreme values, these variables were recoded into a small number of ordered categories. The education categories were 5–9, 10–14, 15–19 and >20 yr. The ISEL categories were <50, 50–74, 75–100 and >100. The ordered variables were then entered into the model as a single covariate, thus assuming that the effect of these variables, if present, would be linear on this ordered scale. To aid in comparison, the PSQ variables were all standardized to have mean 0 and s.e. 1. Thus, the odds ratios calculated for these variables correspond to the effect associated with a change of one sample standard deviation in the variable.

### Results

A total of 184 patients (94.4%) were female. Since there were only a small number of male patients (11), the analysis was restricted to the female patients. Of these female patients, 101 (54.9%) were from the London centre and 83 (45.1%) were from Birmingham; 76.6% were Caucasian, 11.9% were Afro-Caribbean, 9.7% were Asian; 62.1% were married. Median age was 38.9 yr (range 20–80), median disease duration was 9 yr (range 1–39). Median years of full-time education were 12 (range 6–27). Details of patients' employment status and income categories are shown in Table 2. Almost half of the patients did not work and about a third of the patients declared that they did not work because of their lupus. The disease characteristics of these patients are described in Table 3.

The results of fitting the baseline model for the SLICC and the SLAM response variables are presented in Table 4. Longer disease duration and non-Caucasian race appear to be related to damage. There is only a suggestive relationship between race and activity. Very long disease duration and activity appear to be weakly related. No obvious centre effects are evident in this analysis.

Table 5 represents the addition, to the models in Table 4, of the socio-economic variables. The upper section of the table corresponds to adding the variables

TABLE 1. Damage categories

Total SLICC damage	No. of patients (%)
0	80 (43.5%)
1	45 (24.5%)
2	25 (13.6%)
3	19 (10.3%)
4–5	9 (4.9%)
≥6	6 (3.3%)

56.5% of patients had a damage score of ≥1.

TABLE 2. Employment and income categories

Employment status	No. of patients (%)
Full- or part-time work	93 (50.5%)
Not working due to SLE	55 (29.9%)
Not working due to other reasons	36 (19.6%)
Annual personal income of patients who worked (UK £) <sup>a</sup>	
<5000	15 (8.5%)
5000–10 000	15 (8.5%)
10 000–15 000	30 (16.9%)
15 000–20 000	13 (7.3%)
20 000–25 000	8 (4.5%)
>25 000	5 (2.8%)

<sup>a</sup>49.5% of patients did not work.

TABLE 3. Disease characteristics of patients

	Median	Range
SLAM (0-86) (Higher = greater activity)	5	(0-22)
SLICC (0-46) (Higher = greater damage)	1	(0-11)
ISEL (0-120) (Higher = more support)	93	(30-119)
PSQ (Higher = more satisfaction)		
General satisfaction	67	(17-100)
Technical quality	68	(25-100)
Interpersonal satisfaction	75	(25-100)
Communication satisfaction	75	(20-100)
Time spent with doctor	75	(13-100)
Access to care	67	(21-100)

singly and in the latter they are included together. There is some suggestion of a relationship between education and damage. The evidence is stronger when the effect of education is examined after adjusting for the other socio-economic variables. Other analyses indicate that it is the correlation between the ISEL scores and education which is responsible for the change (this analysis is not shown). Thus, there is some indication that higher education levels are associated with less damage. There is no relationship between the socio-economic variables and activity.

Table 6 adds the various satisfaction variables to a model with both the baseline and the socio-economic

variables. When added singly, none of the satisfaction variables demonstrate any relationship with damage or activity. In a multivariate model, when the variables are added together, there is still no relationship between patient satisfaction and activity. However, three of the satisfaction scales, interpersonal, time spent with doctor and access to care, demonstrate significant relationships with damage. Greater satisfaction with interpersonal aspects of care and with access to care are associated with higher levels of damage. Greater satisfaction with time spent with the doctor is associated with lower levels of damage.

The confounding associated with the satisfaction variables, which is evident in these multivariate results, can be illustrated using some simplified variables. Consider a damage variable dichotomized based on a SLICC score of  $>1$  or  $\leq 1$  and satisfaction variables dichotomized as greater or less than the mean. For patients with 'time spent with the doctor' scores less than the mean, a damage rate of 17/54 or 31% is observed for patients with an 'interpersonal' score less than the mean and a rate of 9/12 or 75% is observed for those with an 'interpersonal' score greater than the mean. For patients with 'time spent with the doctor' scores greater than the mean, the same comparison is of damage rates of 4/24 or 17% vs 29/93 or 31% for patients with 'interpersonal' scores less than or greater than the mean, respectively.

Thus, for patients with comparable satisfaction concerning 'time spent with the doctor', the higher damage

TABLE 4. The results of fitting the baseline model for the outcome variables

	SLICC			SLAM			Not working due to lupus		
	OR	CI	P	OR	CI	P	OR	CI	P
Centre									
London	1.00			1.00			1.00		
Birmingham	1.27	(0.73, 2.22)	0.40	0.97	(0.55, 1.73)	0.92	2.42	(1.24, 4.74)	0.01
Race									
Caucasian	1.00			1.00			1.00		
Non-Caucasian	2.15	(1.13, 4.08)	0.02	1.79	(0.92, 3.46)	0.08	1.57	(0.74, 3.36)	0.24
Disease duration									
(<10 yr)	1.00			1.00			1.00		
(10-20 yr)	4.25	(2.31, 7.83)	<0.001	1.06	(0.57, 1.96)	0.86	1.79	(0.87, 3.66)	0.11
(>20 yr)	10.42	(3.92, 27.69)	<0.001	2.69	(1.00, 7.19)	0.05	2.42	(0.79, 7.36)	0.12

OR, odds ratio; CI, 95% confidence interval;  $P \leq 0.05$  was considered significant.

TABLE 5. The results of addition of the socio-economic variables to the baseline model

	SLICC			SLAM			Not working due to lupus		
	OR	CI	P	OR	CI	P	OR	CI	P
Univariate analyses <sup>a</sup>									
Education	0.64	(0.39, 1.05)	0.08	1.17	(0.71, 1.93)	0.54	0.50	(0.27, 0.95)	0.03
ISEL	0.77	(0.55, 1.07)	0.12	0.84	(0.59, 1.19)	0.33	0.76	(0.51, 1.14)	0.19
Marital status	1.37	(0.77, 2.42)	0.23	1.08	(0.60, 1.94)	0.81	1.28	(0.65, 2.55)	0.48
Multivariate analyses <sup>b</sup>									
Education	0.60	(0.36, 0.99)	0.05	1.15	(0.70, 1.90)	0.59	0.51	(0.27, 0.96)	0.04
ISEL	0.76	(0.54, 1.07)	0.11	0.79	(0.55, 1.13)	0.19	0.73	(0.49, 1.11)	0.14
Marital status	1.28	(0.71, 2.29)	0.41	1.05	(0.58, 1.92)	0.87	1.20	(0.59, 2.45)	0.61

<sup>a</sup>Variables added singly to baseline model including centre, race and disease duration.

<sup>b</sup>Variables added together to baseline model.

TABLE 6. The results of addition of the satisfaction variables to a model with both the baseline variables and the socio-economic variables

	SLICC			SLAM			Not working due to lupus		
	OR	CI	P	OR	CI	P	OR	CI	P
Univariate analyses <sup>a</sup>									
General satisfaction	0.86	(0.64, 1.15)	0.32	0.81	(0.60, 1.09)	0.17	0.97	(0.68, 1.38)	0.88
Technical quality	0.87	(0.65, 1.17)	0.35	0.79	(0.59, 1.07)	0.13	0.90	(0.63, 1.28)	0.55
Interpersonal	1.13	(0.85, 1.51)	0.39	0.79	(0.59, 1.06)	0.12	1.19	(0.83, 1.71)	0.35
Communication	0.90	(0.67, 1.21)	0.48	0.77	(0.56, 1.05)	0.09	0.95	(0.66, 1.36)	0.78
Time spent with doctor	0.81	(0.61, 1.10)	0.18	0.76	(0.56, 1.03)	0.07	0.94	(0.66, 1.35)	0.75
Access to care	1.12	(0.83, 1.51)	0.46	1.04	(0.76, 1.40)	0.82	1.23	(0.85, 1.80)	0.27
Multivariate analyses <sup>b</sup>									
General satisfaction	0.70	(0.41, 1.20)	0.20	0.89	(0.51, 1.53)	0.66	0.92	(0.47, 1.80)	0.81
Technical quality	0.79	(0.44, 1.39)	0.41	0.93	(0.52, 1.67)	0.81	0.56	(0.26, 1.17)	0.12
Interpersonal	2.40	(1.37, 4.19)	0.002	1.02	(0.58, 1.79)	0.96	2.48	(1.20, 5.13)	0.02
Communication	0.77	(0.45, 1.34)	0.36	0.87	(0.49, 1.55)	0.64	0.74	(0.37, 1.46)	0.38
Time spent with doctor	0.60	(0.39, 0.94)	0.03	0.76	(0.48, 1.20)	0.24	0.77	(0.45, 1.33)	0.35
Access to care	1.53	(1.01, 2.30)	0.04	1.44	(0.95, 2.20)	0.09	1.59	(0.93, 2.71)	0.09

<sup>a</sup>Variables added singly to model with baseline variables and socio-economic variables.<sup>b</sup>Variables added jointly to model with baseline variables and socio-economic variables.

rates are seen in those with the highest satisfaction with 'interpersonal' aspects of their care. Also, for patients with comparable satisfaction with 'interpersonal' aspects of their care, the lower damage rates were seen in patients with the highest levels of satisfaction with 'time spent with the doctor'. The correlation between these different areas of satisfaction is evidenced by the fact that 93/111 or 79% of those satisfied with their 'time spent with doctor' were satisfied with 'interpersonal' relationships, whereas only 12/66 or 18% of those dissatisfied with 'time spent with the doctor' were satisfied with 'interpersonal' relationships. Failure to adjust for this correlation in the univariate analyses accounts for the different results found in these analyses compared with the multivariate analysis.

Table 7 represents a final model when all the variables are entered altogether. When SLAM scores are added into the SLICC model in the final step, the association between education and damage becomes stronger ( $P = 0.04$ ). There is also an association between higher disease activity and more damage. The addition of SLAM scores into the final model does not affect the qualitative results. However, the estimated coefficient relating access to care to damage becomes slightly smaller and the associated  $P$  value for the test for an association between damage and access to care changes from 0.04 to 0.09. There is also an apparent centre effect after adjustment for socio-economic, patient satisfaction variables and the SLAM.

Tables 4, 5 and 6 also present results for the 'not working due to lupus outcome'. Patients from Birmingham and patients with a lower level of education were more likely to be not working due to their lupus. Otherwise, the results are similar to those based on the SLICC scores, although only the association between more satisfaction with interpersonal aspects of care and not working due to lupus achieves significance. When SLAM scores are added into the final model, there is

also an association between higher disease activity and not working due to lupus.

## Discussion

This study shows that patients of non-Caucasian origin, with longer disease duration, lower level of education and higher disease activity, are more likely to have end-organ damage.

It has long been known that patients of Afro-Caribbean and Asian origin are at more risk of developing SLE and they tend to have more severe disease [20, 21]. It has, however, been difficult to separate the effects of race from socio-economic status, especially in countries like the USA where access to health care is closely linked to income. Some studies show that American Blacks have a poorer survival than White patients do and this is not due to their socio-economic status [22]. In contrast, in other studies, the association between increased mortality and Black race appears to be related to socio-economic status, which is poorer among Blacks [23]. The discrepancy between these studies may be partly due to the use of unstable measures of socio-economic status, like insurance status. We have confirmed in this study that non-Caucasian patients who, in theory, have equal access to health care as Caucasian patients in the UK, still accumulate more organ damage and this is independent of their level of education. We have also shown that lower level of education is a separate risk factor for organ damage.

We have considered the educational level to be an indicator of socio-economic status in this study. Educational level has previously been shown to be a more stable determinant of socio-economic status compared to other factors like insurance status or income, which change with time and disease onset [24]. Although we have assessed patients' employment status and income, this was done at the time of damage assessment.

TABLE 7. The results of fitting the final model for all the outcome variables

	SLICC			SLAM			Not working due to lupus		
	OR	CI	P	OR	CI	P	OR	CI	P
Centre									
London	1.00			1.00			1.00		
Birmingham	2.06	(1.10, 3.86)	0.02	1.15	(0.61, 2.16)	0.66	3.94	(1.65, 9.38)	0.002
Race									
Caucasian	1.00			1.00			1.00		
Non-Caucasian	2.29	(1.12, 4.71)	0.02	1.70	(0.83, 3.51)	0.15	2.03	(0.78, 5.26)	0.15
Disease duration									
< 10 yr	1.00			1.00			1.00		
10–20 yr	5.20	(2.67, 10.11)	<0.001	0.85	(0.44, 1.64)	0.63	2.23	(0.92, 5.43)	0.08
> 20 yr	9.61	(3.51, 26.36)	<0.001	2.40	(0.88, 6.54)	0.09	1.70	(0.45, 6.42)	0.44
Education	0.56	(0.33, 0.96)	0.04	1.16	(0.69, 1.96)	0.57	0.45	(0.21, 0.94)	0.03
ISEL	0.82	(0.56, 1.19)	0.30	0.82	(0.56, 1.20)	0.30	0.81	(0.49, 1.33)	0.40
Marital status	1.19	(0.65, 2.18)	0.57	0.92	(0.50, 1.72)	0.80	1.16	(0.51, 2.61)	0.73
General satisfaction	0.72	(0.42, 1.23)	0.23	0.89	(0.51, 1.53)	0.66	0.91	(0.44, 1.91)	0.81
Technical quality	0.80	(0.45, 1.42)	0.44	0.93	(0.52, 1.67)	0.81	0.55	(0.25, 1.23)	0.15
Interpersonal	2.44	(1.39, 4.27)	0.002	1.02	(0.58, 1.79)	0.96	2.91	(1.29, 6.57)	0.01
Communication	0.79	(0.45, 1.37)	0.40	0.87	(0.49, 1.55)	0.64	0.79	(0.38, 1.63)	0.52
Time spent with doctor	0.63	(0.40, 0.98)	0.04	0.76	(0.48, 1.20)	0.24	0.79	(0.43, 1.45)	0.45
Access to care	1.43	(0.95, 2.17)	0.09	1.44	(0.95, 2.20)	0.09	1.35	(0.76, 2.41)	0.30
SLAM									
(0–4)	1.00			–			1.00		
(5–10)	1.62	(0.87, 3.02)	0.13	–			4.94	(2.09, 11.69)	<0.001
(> 10)	2.68	(1.06, 6.80)	0.04	–			15.59	(4.26, 57.07)	<0.001

Ideally, we would have liked to know about these facts prior to disease onset, although there would be a recall bias and we could not be sure about the accuracy of the information given after many years of disease.

At the time of study, almost half of the patients did not work and about a quarter of these patients did not declare their income (in comparison to 7% of employed patients who did not declare their income). Since there was so much missing data on income, it was not included in the analyses. Information on employment status was complete (Table 2). About a third of the patients declared that they were not working due to their lupus. Patients with a lower level of education were more likely not to be working due to their lupus. Since the prospects of employment would be expected to be worse for the less educated even in the absence of illness, this finding was not surprising. Patients from Birmingham were also more likely to be not working due to their disease, perhaps due to relatively more adverse economic circumstances. Other factors may have played a part in determining the employment status of those patients. Not surprisingly, patients with higher disease activity were also more likely not to be working due to their lupus.

Longer disease duration and, to a lesser extent, higher disease activity were both associated with more damage in this study. It has previously been shown by Karlson *et al.* [7] that cumulative damage is strongly associated with non-modifiable clinical factors such as older age at diagnosis, longer disease duration, nutrition and higher disease activity. They did not find any relationship between race, socio-economic status and damage, which is in contrast to our study. Their study was conducted in the USA which has a different social, education and health care system. Their cohort was also somewhat

different from ours. They had a higher percentage of Afro-Caribbean patients (52% vs 11.9% in our study). Their patients were also younger (mean age 37.6 vs 40.3 yr) and had a shorter duration of disease (mean disease duration 3.8 vs 10.3 yr). The percentage of unemployed patients was 7% (at diagnosis) and 16% (at study visit) in their cohort vs 49.5% at study visit in ours. All these factors may have a role in explaining the discrepancies between the two studies.

Multivariate analyses also showed associations between damage and some aspects of patient satisfaction with care. Patients with more damage were more satisfied with interpersonal aspects of their care (e.g. courtesy and respect) and their access to care (how easily and quickly they can be seen in clinic, get medical care in an emergency or be admitted), but less satisfied with the amount of time they spent with their doctor. Patients who were not working due to their disease were also more satisfied with the interpersonal aspect of their care. Although it is difficult to predict the direction of these relationships, these results probably imply that patients with more damage need to spend more time with their doctors either during a consultation or during treatment, and this aspect of our care needs improvement. These results partly reflect our practice and partly reflect our patients' expectations.

There was weak evidence for an association between very long disease duration and higher disease activity at the time of assessment. Other variables including socio-demographic, socio-economic and patient satisfaction variables did not appear to be correlated with disease activity. Karlson *et al.* [24] previously showed that having higher education and private insurance or Medicare were the best predictors of less disease activity

at diagnosis. We have studied the relationship between education level and disease activity at the time of study and failed to show any significant relationship. Karlson *et al.* also showed that race is not significantly associated with disease activity at diagnosis, even when other socio-economic factors are considered. In our study, there was only a suggestion of a relationship between non-Caucasian race and higher disease activity. In a similar cohort, they have also shown that younger age at diagnosis and psychosocial factors like lower self-efficacy for disease management and less social support were associated with greater disease activity at study visit [7]. We did not confirm this relationship between social support and disease activity.

In a recent study, Reveille *et al.* [25] studied the impact of immunogenetic and socio-economic factors on SLE in three different ethnic groups (Caucasians, African-Americans and Hispanics). They have shown that African-American and Hispanic patients and patients with less education have higher disease activity at disease onset. They have also shown an association with HLA status. These authors also studied the same cohort early in the course of their SLE (disease duration  $\leq 5$  yr) and showed an association between disease activity and African-American ethnicity, lack of private health insurance, as well as other clinical, immunological, immunogenetic, behavioural and psychological variables [26]. Some of the discrepancies between studies may be due to the assessment of disease activity at different time points during the course of disease (at disease onset vs early or late in the course of SLE) or different health care and education systems.

In summary, end-organ damage was increased in patients of non-Caucasian race and low socio-economic status. Other predictors of damage included clinical factors like disease duration and activity, and also some aspects of satisfaction with care. In contrast, increased disease activity was only associated with long disease duration and none of the sociodemographic, socio-economic or psychosocial factors were predictive of disease activity in this cross-sectional study. As well as controlling disease activity by conventional treatment, improving the level of education may reduce end-organ damage in patients with SLE.

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# Emergency department utilization by HIV-positive adults in the HAART era

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## Abstract

**Background** No published study has analyzed emergency department (ED) utilization by human immunodeficiency virus (HIV)-positive adults in the highly active antiretroviral therapy (HAART) era.

**Aims** The purpose of this study is to describe the demographic and HIV-specific variables associated with ED utilization by HIV-positive adults and their diagnoses when discharged from the ED or subsequently from the hospital.

**Methods** We conducted a retrospective cohort study of all HIV-positive adults cared for at a tertiary center HIV clinic and ED (1 January–31 December 2006). Demographic, HIV clinical, and HIV lab variables were abstracted from the clinic database. ED/hospital diagnoses coded by the

ICD-9 Diseases/Injuries Tabular Index were abstracted from identified discharge records. We used multivariate logistic regression to compute odds ratios (OR) of ED utilization based on the abstracted variables. We described the cohort and diagnoses using descriptive statistics.

**Results** A total of 356 patients met inclusion criteria. Their mean age was 42.7 years, and 77.2% of included patients were male; 52.5% were Caucasian and 47.5% non-Caucasian; 72 patients (20.2%) presented to the ED during the study period [153 visits; 37 (10.4%) required hospitalization (61/153 visits)]. Income level and mean 2006 viral load had a significant association ( $p < 0.05$ ) with ED utilization. Of 155 ICD-9 ED discharge diagnoses, ill-defined symptoms/signs (25.2%), injury (18.7%), and musculoskeletal disorders (11.6%) were most prevalent. Of 450 ICD-9 hospital discharge diagnoses, endocrine/metabolic (13.3%), psychiatric (12.2%), infectious/parasitic (12%), and circulatory disorders (11.8%) were most prevalent.

**Conclusion** In this study of HIV-positive adults, income level and mean 2006 viral load had a significant association with ED utilization. Noninfectious diagnoses were alone most prevalent in ED discharged, but not hospitalized, patients.

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Since the conduct of this study, Dr. Piontkowsky has left the employ of Allegheny General Hospital and now works for Pfizer Pharmaceuticals.

The views expressed in this paper are those of the author(s) and not those of the editors, editorial board or publisher.

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## Introduction

### Background

The World Health Organization estimates that as of December 2007, 33.2 million individuals are infected with human immunodeficiency virus (HIV), with 2.5 million

individuals becoming newly infected in the previous 12 months [1]. With the advent of highly active antiretroviral therapy (HAART), HIV-infected adults have experienced an increase in life expectancy. One study has quantified the mean increase in life expectancy for a 20-year-old HIV-infected adult as rising from 9.1 years (+2.3 years) in 1993–1995 to 23.6 years (+4.4 years) in 2002–2004 [2]. This increase in life expectancy, largely attributable to HAART [3], has also resulted in a changing spectrum of illness for HIV-positive adults. Recent studies from the HAART era where patients have access to such medications have found that hospitalizations due to opportunistic infections, especially late-stage conditions such as *Cryptosporidium* and *Mycobacterium avium*, have decreased while those related to cardiovascular disease, medication side effects, and malignancies have increased [4, 5]. This pattern stands in contrast to the pre-HAART era when opportunistic infections comprised over 23% of hospital discharge diagnoses, with an additional 10.1% due to respiratory ailments, predominantly pneumonia of an uncharacterized nature [6].

To our knowledge, no published study has analyzed what factors are specifically associated with emergency department (ED) utilization by HIV-infected adults in the HAART era. Similarly, while previous studies have focused on the pattern of inpatient discharge diagnoses among HIV-positive adults [5, 7], the nature of ED and hospital discharge diagnoses in HIV-infected adults who present to the ED has not specifically been examined. Previous articles in the emergency medicine literature have emphasized the treatment of opportunistic infections in the HIV-infected population [8–10]. While one previous study based on ED presentation found that HIV-infected patients often were diagnosed with conditions unrelated to their HIV status, their patient population was examined in the pre-HAART era, though published in 1997 [11]. The changing spectrum of illness in HIV patients requires emergency physicians to have a better understanding of the conditions that can bring HIV patients to the ED and require hospitalization [12]. Previous studies have shown that attempts to develop triage instruments for HIV-positive patients have poor sensitivity and specificity for emergent versus nonemergent conditions, supporting the need for a better understanding of why and how HIV-positive patients present for emergency care [13]. It would also be useful to both emergency physicians and infectious disease specialists to determine if preventable factors are associated with ED utilization that can be addressed in the outpatient setting.

#### Study purpose and hypotheses

The purpose of this study is to describe the demographic and HIV-specific variables currently associated with ED

utilization by HIV-positive adults and to describe their diagnoses when discharged from the ED or subsequently from the hospital. We hypothesized that for HIV-positive adults in the HAART era, demographic [age, sex, race, and income level relative to the federal poverty line (FPL)], not HIV-specific clinical (years since diagnosis/on antiretroviral therapy, 2006 use/interruption of HAART) or laboratory (recorded peak and mean 2006 viral load/nadir and mean 2006 CD4 count) factors are significantly associated with ED utilization within this population. We also hypothesized that, with the availability of the improved means to control HIV through HAART, noninfectious ED/hospital discharge diagnoses are most prevalent among HIV-positive adults who present to the ED.

## Methods

### Study design

This was a retrospective, observational cohort study of all HIV-positive adults followed in a federally supported HIV clinic located in an urban, level 1 trauma tertiary care center from 1 January 1 to 31 December 2006. The study was approved by the Institutional Review Board for this center.

### Setting

The study center is a level 1 trauma tertiary care referral center with an ED that sees approximately 50,000 patients per year. The center is located in a county with an estimated prevalence of acquired immunodeficiency syndrome (AIDS) patients between 50–165/100,000 residents [14]. The dedicated HIV clinic in this center is governmentally supported and is a referral center for the region for HIV-infected adults, with treatment provided to local patients as well as those from adjacent states.

### Study population and inclusion/exclusion criteria

All HIV-positive adults followed in this center's HIV clinic between 1 January and 31 December 2006 were included in this study. These individuals were identified from a preexisting database maintained by the clinic for outpatient management. Demographic, clinical history, and laboratory information on these patients is entered into this database by treating physicians and nurses and maintained by a program coordinator for the clinic.

### Definition of clinical variables

Age was calculated as that on 1 January 2006. Some included patients did not have viral load or CD4 count

testing during the study period, either due to presenting late in 2005 and not having follow-up until early 2007, having been diagnosed in 2006 and not having HIV-related lab testing until early 2007, or only having one clinic visit during the study period and not undergoing serum testing as prescribed. For these study subjects, these variables were treated as unknown. Viral loads (copies/ml) were classified as either <400, 401–1,000, 1,001–100,000, or >100,000. Previous studies have found that increases in viral load from undetectable to higher levels are associated with adverse outcome and that categorization of viral load similar to these cutoffs was associated with increased risk of progression to AIDS in HIV-infected adults [15, 16]. CD4 counts (cells/ml) were classified as <200, 201–350, and >350 based on existing guidelines for initiation of HAART to decrease the risk of developing AIDS and AIDS-defining illnesses [17].

All ED and hospital discharge diagnoses were included for analysis as to the prevalence of particular ICD-9 Diseases/Injuries Tabular Index categories during the study period in ED and hospital discharged HIV-infected adults. The only diagnoses excluded from analysis were those coded under the ICD-9 classification as V or E. These codes are used in the ICD-9 classification to provide context to the more specific diagnosis given. Diagnoses coded V50–V59, indicating encountering of health personnel for specific procedures and aftercare, were included for analysis. Previous studies examining HIV-related hospitalizations have only included the first four coded hospital discharge diagnoses [6]. However, as the abstracting investigators for this part of the study were not the treating physicians for these patient visits, it was felt that selection bias was best avoided by including all coded diagnoses for each ED visit.

#### Data collection and processing

The investigators created a standardized case report form that was used to abstract the specific demographic and HIV-specific variables described above in included study subjects. The study subjects were identified from the preexisting clinic database described above. The case report form also was used to record whether a subject was seen in the ED, was subsequently admitted to the hospital, and what their ICD-9 coded ED and hospital discharge diagnoses were. Demographic (age on 1 January 2006, sex, race, and income level relative to FPL), HIV clinical (years since HIV diagnosis, years on any antiretroviral therapy, use of HAART during 2006, and interruption of HAART during 2006), and HIV laboratory variables (highest viral load on record to 31 December 2006, mean viral load during 2006, lowest CD4 count on record to 31 December 2006, and mean CD4 count during 2006) were

chosen for abstraction based on the theoretical framework outlined above. One investigator and the clinic's program coordinator jointly abstracted this information to the standardized case report form. The investigator and clinic program coordinator were not blinded to the study's purpose.

The center's information services department, which maintains a database of this center's medical and discharge billing records, was queried as to whether the identified HIV-infected patients meeting inclusion criteria had presented to the ED during the study period. The information services department provided a list of ED visit dates, whether the patient was discharged from or admitted to the hospital, and ICD-9 coded ED and hospital discharge diagnoses for each patient who presented to the ED. Two investigators concurrently abstracted this information to the case report form and classified these diagnoses using the ICD-9 Diseases/Injuries Tabular Index, which has been used in previous studies to analyze the characteristics of hospital discharge diagnoses in HIV-infected patients [6, 18]. Data from the case report forms were then entered by the investigators into a Microsoft Excel (Microsoft Office for Windows XP, Redmond, WA, USA) spreadsheet, and range and consistency checks were performed to verify accuracy of data entry.

#### Outcome measures

The primary outcome measure in this study was whether an HIV-infected adult followed at this center's HIV clinic during the study period utilized the ED. The analytic strategy was designed to identify whether demographic, HIV clinical, or HIV laboratory variables distinguished those who presented to the ED from those who did not. A secondary dependent variable was a descriptive classification of ED and hospital discharge diagnoses in those HIV-infected patients who presented to the ED, as classified by the ICD-9 Diseases/Injuries Tabular Index.

#### Statistical analysis

Descriptive statistics (percents, means, and standard deviations) were used to characterize the demographic and HIV-specific characteristics of the included subjects. We used SPSS for Windows v. 15.0 (Chicago, IL, USA) to create a multivariable logistic regression model and compute odds ratios (OR) with 95% confidence intervals (95% CI) for the association of the specific demographic, HIV clinical, and HIV laboratory variables abstracted and the likelihood of ED utilization within the cohort from those who did not present to the ED. Given the presence of missing data, we used a  $\chi^2$  analysis (SPSS for Windows v. 15.0, Chicago, IL, USA) to determine if those patients with missing data were differentially more or less likely to present to the ED.

To analyze the prevalence of ED and hospital discharge diagnostic categories within the ICD-9 Diseases/Injuries Tabular Index for those cohort patients who presented to the ED, we calculated the percentage of each ICD-9 diagnostic category using Microsoft Excel (Microsoft Office for Windows XP, Redmond, WA, USA).

## Results

### Characteristics of study subjects

Table 1 provides a summary of the characteristics of subjects that met inclusion criteria during the study period and the distribution of variables analyzed in this project. A total of 356 HIV-positive adults were followed at the center's clinic during the study period of 1 January–31

December 2006. Overall, the study cohort was 77.2% male with a mean age of 42.7 (standard deviation:  $\pm 8.5$  years); 52.5% of the cohort were Caucasian, 46.1% were black, and 1.4% were of a different minority race (Asian, Hispanic, or Native American). For analytic purposes ethnicity was dichotomized (Caucasian vs non-Caucasian) due to the low frequency of individuals of a racial minority other than black. Seventy-two patients (20.2%) presented to this center's ED during the study period a total of 153 times. Thirty-seven patients (10.4%) in the cohort were admitted to the hospital from the ED. Of the 153 total visits, 61 (39.9%) resulted in hospital admission.

### Main results

Table 2 shows the results of the multivariable logistic regression model that analyzed the association of demo-

**Table 1** Demographic and HIV-specific characteristics of the patient cohort

Demographic or HIV-specific variable	Full sample (N=356)	No ED visit (N=284)	ED visit (N=72)
Mean age (SD)	42.7 (8.5)	42.8 (8.7)	41.9 (7.6)
Gender (% male)	77.2	77.8	75.0
Income level (%)			
Below poverty level	45.8	40.8	65.3
1–2× poverty level	24.7	25.4	22.2
2–3× poverty level	12.4	13.0	9.7
>3× poverty level	14.0	17.3	1.4
Not recorded	3.1	3.5	1.4
Race (% non-Caucasian)	47.5	45.1	56.9
Mean years since HIV diagnosis (SD)	8.5 (5.9)	8.2 (5.9)	9.8 (5.8)
Mean years on antiretroviral therapy (SD)	3.5 (3.2)	3.6 (3.3)	2.9 (3.0)
On HAART in 2006 (% yes)	81.5	82.4	77.8
HAART interrupted/discontinued in 2006 (% yes)	7.3	6.3	11.1
Peak viral load on record, copies/ml (%)			
<400	18.0	19.0	13.9
401–1,000	2.2	2.4	1.4
1,001–100,000	36.2	37.0	33.3
>100,000	38.5	37.7	41.7
Unknown	5.1	3.9	9.7
Mean viral load in 2006, copies/ml (%)			
<400	53.1	57.4	36.1
401–1000	2.8	3.1	1.4
1,001–100,000	19.9	18.0	27.8
>100,000	9.3	8.1	13.9
Unknown	14.9	13.4	20.8
Lowest CD4 count on record, cells/ml (%)			
0–200	41.3	40.5	44.4
201–350	25.8	26.8	22.3
>350	28.4	29.6	23.6
Unknown	4.5	3.1	9.7
Mean CD4 count in 2006, cells/ml (%)			
0–200	13.8	13.0	16.7
201–350	17.4	16.9	19.4
>350	54.5	57.4	43.1
Unknown	14.3	12.7	20.8

**Table 2** Odds ratios of likelihood of emergency department utilization based on abstracted demographic and HIV-specific variables

Demographic/HIV-specific variable	Referent value (if applicable)	Odds ratio	95% confidence interval	<i>p</i> value
<b>Demographic variable</b>				
Age		0.99	0.95–1.03	0.56
Sex	Female	1.36	0.63–2.94	0.44
Race	Non-Caucasian	0.74	0.38–1.42	0.36
Income level (1–2× FPL)	Income level (<FPL)	0.58	0.27–1.24	0.16
Income level (2–3× FPL)		0.36	0.12–1.09	0.07
Income level (>3× FPL)		0.07	0.008–0.52	0.01
<b>HIV clinical variable</b>				
Years since HIV diagnosis		1.05	0.98–1.11	0.16
Years on HAART		1.01	0.89–1.15	0.89
On HAART in 2006	Yes	0.54	0.17–1.75	0.31
HAART Interrupted in 2006	Yes	1.66	0.48–5.72	0.42
<b>HIV laboratory variable</b>				
Highest viral load on record (401–1,000)	Highest viral load on record	0.93	0.09–9.73	0.95
Highest viral load on record (1,001–100,000)	(<400 copies/ml)	0.93	0.30–2.86	0.90
Highest viral load on record (>100,000)		0.81	0.24–2.74	0.74
Mean viral load in 2006 (401–1,000)	Mean viral load in 2006 (<400 copies/ml)	0.79	0.08–7.12	0.79
Mean viral load in 2006 (1,001–100,000)		3.49	1.26–9.73	0.02
Mean viral load in 2006 (>100,000)		5.43	1.39–21.21	0.02
Lowest CD4 count on record (0–200)	Lowest CD4 count on record (>350 cells/ml)	1.14	0.36–3.57	0.82
Lowest CD4 count on record (201–350)		0.87	0.33–2.27	0.77
Mean CD4 count in 2006 (0–200)	Mean CD4 count in 2006 (>350 cells/ml)	0.61	0.18–2.07	0.43
Mean CD4 count in 2006 (201–350)		0.97	0.35–2.69	0.95

graphic, HIV-specific clinical, and HIV-specific laboratory variables with ED utilization. Sixty-three patients had missing data, and analysis of this group compared to those with complete data (293 patients) did not reveal differentially greater or lesser likelihood of ED presentation [ $\chi^2$  ( $df=1$ )=1.27,  $p=0.26$ ]. The full model for the 293 patients with complete data was significantly reliable [ $\chi^2$  ( $df=20$ )=35.23,  $p=0.02$ ] and accounted for between 11.3 and 18.2% of the variance in ED presentation status. Income level greater than 3× the FPL was the only demographic variable with a significant association with ED utilization, showing a decreased likelihood of presenting to the ED [OR: 0.07 (95% CI: 0.01–0.52)]. Those subjects with an income 2–3× the FPL also showed a trend towards lesser likelihood of ED utilization, though not reaching statistical significance [OR: 0.36 (95% CI: 0.12–1.09)]. No other demographic variable (age, sex, or race) showed a significant association with ED utilization in the study cohort.

Among the HIV-specific clinical and laboratory variables, higher mean viral load during the study period was associated with increased odds of ED utilization within the study cohort, contrary to our hypothesis that only demographic variables would show a significant association with ED use. Those with a mean viral load of 1,001–100,000 copies/ml during 2006 were 3.49 times more likely to present to the ED when compared to those with low viral

loads ( $p=0.02$ , 95% CI: 1.26–9.73). Similarly, those with very high mean viral loads (>100,000 copies/ml) during 2006 were 5.43 times more likely to present to the ED when compared to those with low viral loads ( $p=0.02$ , 95% CI: 1.39–21.21). No other HIV-specific variables were related to ED utilization.

Figure 1 provides a graphical representation of the distribution of ED discharge diagnoses in the 92 ED visits that did not result in hospital admission. Of the 155 ICD-9 coded ED discharge diagnoses, the most prevalent categories were ill-defined symptoms/signs (25.2% of all ED discharge diagnoses), injury specifically within the category of injury/poisonings (18.7% injury/1.3% poisonings), and musculoskeletal disorders (11.6%). Infectious/parasitic diagnoses represented 4.5% of all ED discharge diagnoses, primarily related to herpes simplex, viral syndromes (two diagnoses each), thrush, and warts (one diagnosis each). Within the category of ill-defined symptoms/signs, diagnoses of abdominal pain not otherwise specified (NOS) (seven diagnoses), diarrhea (five diagnoses), vomiting, chest pain NOS, and convulsion (possible seizure) (four diagnoses each) were most prevalent.

Figure 2 provides a graphical representation of the distribution of hospital discharge diagnoses in the 61 ED visits that resulted in hospital admission. Of the 450 ICD-9 coded hospital discharge diagnoses, the most prevalent

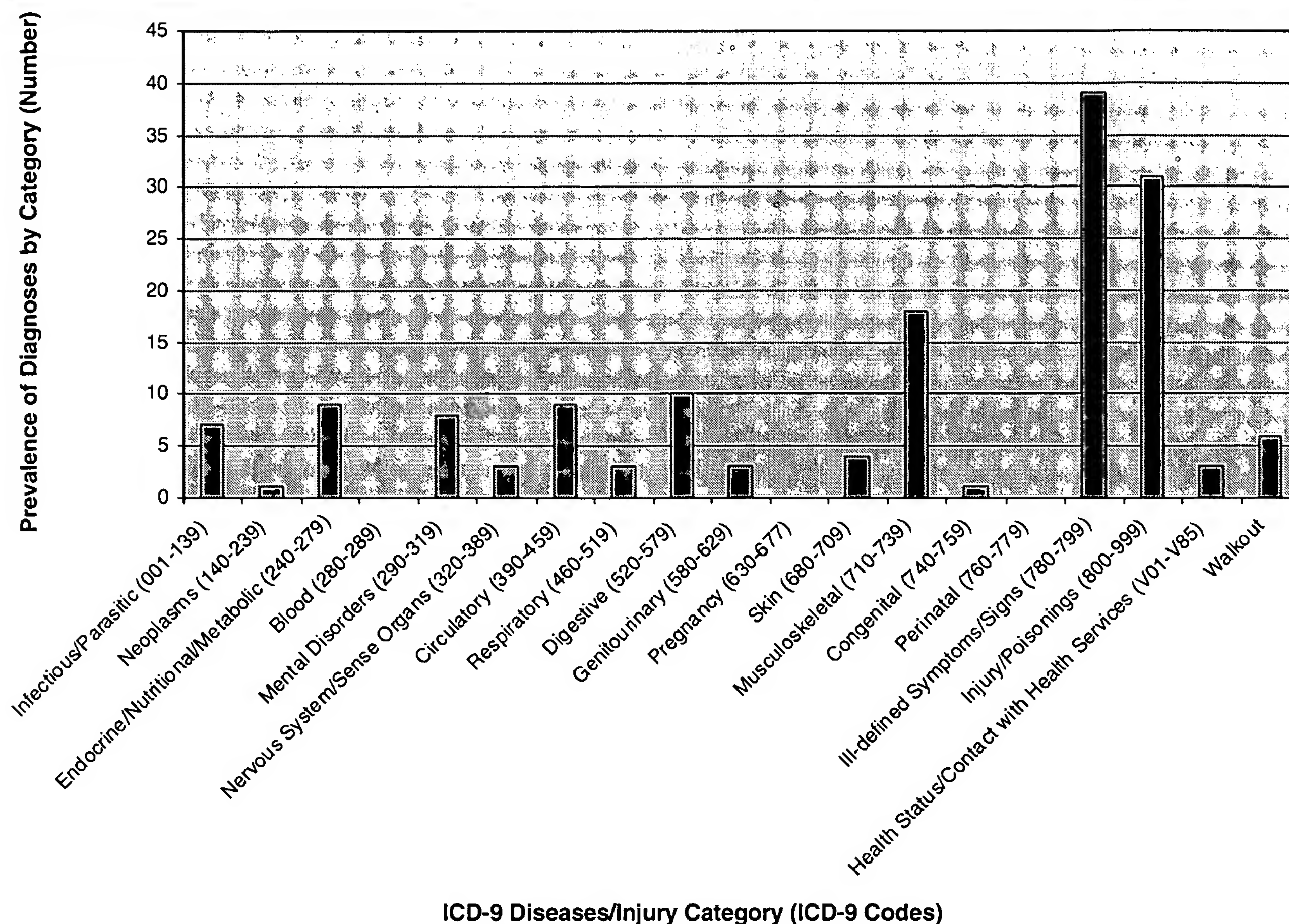


Fig. 1 Prevalence of emergency department discharge diagnoses

categories were endocrine/metabolic (13.3% of all hospital discharge diagnoses), psychiatric (12.2%), infectious/parasitic (12%), and circulatory disorders (11.8%). Within the category of infectious/parasitic disorders, diagnoses related to thrush (12 diagnoses) and hepatitis C (7 diagnoses) were most prevalent. The most common endocrine/metabolic diagnoses were related to an electrolyte abnormality (14 diagnoses) and diabetes mellitus (14 diagnoses). Among psychiatric diagnoses, substance abuse (22 diagnoses) and depression (20 diagnoses) were most prevalent. In the circulatory disorders category, the most common diagnosis related to cardiomyopathy/congestive heart failure (11 diagnoses).

## Discussion

This study's results show that ED utilization among HIV-positive adults in the HAART era was associated with a lower income level and greater mean viral load during the study period and that infectious/parasitic diagnoses continue to be among the most prevalent among hospitalized, though not ED discharged, HIV-infected adults. However,

there are a number of limitations that affect the generalizability of these findings. This center resides in a region with a low prevalence of HIV in comparison to other major urban centers, both within the country and worldwide [14]. For centers in higher prevalence areas, the diagnoses distribution and variables associated with ED utilization may be different due to other epidemiological factors, such as lack of knowledge of underlying HIV status and lack of access to clinical resources to manage HIV. Such factors should be addressed in future studies that are larger scale and have the ability to differentiate and follow patients found to be HIV-positive after ED visits suspected to be related to HIV.

In addition, larger epidemiological studies with greater sample sizes may indicate that other demographic and HIV clinical/laboratory variables are associated with ED utilization by this patient population. This study, as such, is preliminary and should be used to guide further evaluation of ED utilization by HIV-positive adults on a multicenter basis.

The retrospective methodology used does not allow the investigators to control for other comorbid conditions that might affect the prevalence of diagnoses in this cohort or as

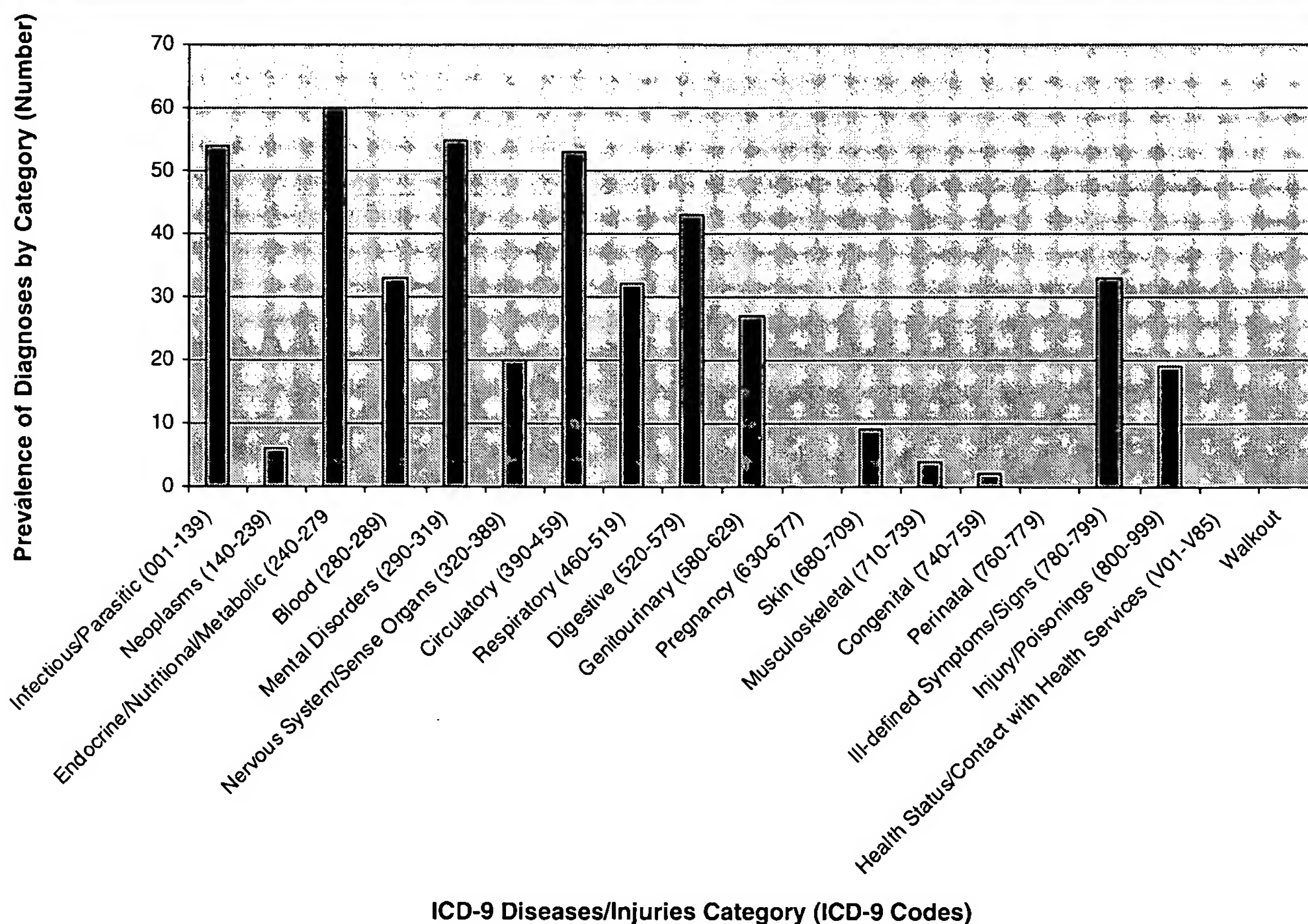


Fig. 2 Prevalence of hospital discharge diagnoses

a confounding variable of ED utilization. Similarly, the retrospective methodology does not allow for the ability to determine the accuracy of all ascribed ED and hospital discharge diagnoses in this cohort. Any attempt to do so by the study investigators would introduce significant selection bias into these findings, and, as discussed above, previous studies on this topic have not controlled for these two factors [6].

Finally, the analysis of ED utilization in this cohort (Table 2) is limited to those patients with complete data to allow multivariable logistic regression. Sixty-three patients had missing data, primarily related to CD4 count and viral load during the study period. This often was related to patients who were followed in the center's HIV clinic during the study period, but did not require lab testing per the treating physicians, having been seen late in 2005 and not requiring follow-up until 2007, having been diagnosed with HIV in 2006 and not having lab testing related to that diagnosis until early 2007, or due to patient nonadherence with prescribed lab testing during the study period. This limitation would likely apply to any retrospective study on the subject. However, our analysis of these 63 patients, in

comparison to the 293 patients with complete data, did not reveal that they were differentially more or less likely to present to the ED. A prospective study may limit this factor, but would introduce the bias of investigator knowledge of the purpose of the study and potentially result in overly careful monitoring of patients in the outpatient setting and decreased use of the ED beyond what is found in this type of observational study.

This study presents the first attempt to determine what variables are specifically associated with ED utilization by HIV-positive adults during the HAART era as well as an analysis of ED and hospital discharge diagnoses of those who presented to the ED for care. The findings that income level and mean viral load during the study period had a significant association with ED utilization supports previous studies that have found that a combination of demographic considerations and health status are in general associated with frequent ED users [19, 20]. Specifically related to HIV, previous studies evaluating outpatient and inpatient utilization in the HIV-positive adult population have found that demographic and HIV-specific factors are associated with increased requirements of inpatient resour-

ces. Fleishman et al. found that black patients, female patients, and those with worsening immunosuppression, as determined by either CD4 count or viral load, were more likely to require inpatient care in the HAART era [21]. Floris-Moore et al. found that female sex and not being on HAART increased the risk of hospitalization among HIV-positive adults [22].

Our study, in contrast, did not find that race or gender had a significant association with ED utilization. That income level was the only demographic variable found to be associated with ED utilization in this study raises the likelihood that either those with higher incomes, due to having better access to outpatient and primary care, had less need for emergency services or that they sought emergency care in other centers unless feeling they would require hospitalization. There is evidence from the pre-HAART era that racial disparities associated with ED utilization by HIV-positive adults in that period were partially explained by the lack of access to outpatient resources such as substance abuse rehabilitation and home health care [23].

The finding that mean viral load during the study period alone was associated with ED utilization among HIV-specific factors suggests that this factor should be further evaluated by infectious disease and emergency physicians as a target for preventing the need for emergency care. Previous studies have come to differing conclusions about the relative importance of viral load versus CD4 count in prognosis of HIV-infected patients. MacArthur et al. found that CD4 count more than viral load had a significant association with progression to AIDS or death [24]. In contrast, Mellors et al. found that increasing viral load was associated with risk of dying of AIDS though the combination of viral load and CD4 count were most predictive of this adverse outcome [16]. The result in our study that increasing mean viral load, and not decreasing CD4 count, was associated with ED utilization may indicate that viral load is a better surrogate marker for acute illness requiring emergency care while CD4 count is a better marker for long-term outcome, such as death or developing AIDS-defining illness. Larger epidemiological studies of known HIV-positive patients should further evaluate this finding.

This investigation did not consider insurance status as a potential variable associated with ED utilization. As this study center is supported by governmental funding, patients treated at the clinic, if not fully covered by private or public insurance, had access to treatment medications through this program. Income level, taken from patient report to the clinic, is an easy financial marker tracked by the clinic database that can be used to determine how socioeconomic status affects the likelihood of ED use. This variable is also more readily considered in practice settings where insur-

ance status is not an issue due to single-payer health systems.

The investigators also did not consider methods of HIV transmission as a variable affecting ED utilization. We had no logical construct as to how transmission status—whether sexual, intravenous drug use, or blood transfusion/professional exposure—would relate to presentation in the ED setting. Fleishman et al. found that adults infected with HIV through intravenous drug use were more likely to require inpatient, though not outpatient, resource use, but could not distinguish whether this was due to ongoing substance abuse [21]. The result in our investigation that psychiatric diagnoses, specifically those related to substance abuse, are the second most prevalent hospital discharge diagnoses suggests that ongoing drug use, as opposed to means of transmission, is more important as a risk factor for ED presentation and inpatient care.

This investigation represents the first study, to our knowledge, that has specifically analyzed the character of ED diagnoses in HIV-infected adults during the HAART era who are discharged after care in the ED. The finding that ill-defined signs and symptoms (Fig. 1) are most prevalent may represent a bias among treating emergency physicians to rule out life-threatening diagnoses and characterize discharged patients in the broadest sense (chest pain or abdominal pain NOS, for example). At the same time, given the association of increased viral load with ED utilization, it is also likely that these ill-defined symptoms/signs represent patient complaints that are potentially related to poor control of their underlying systemic infection or side effects from complex medication regimens. Other studies have found that hospitalizations specifically related to medication side effects have increased in the HAART era [4, 5]. The use of ICD-9 coding and classification would not easily allow examination of whether particular diagnoses were related to HAART regimens or not. The finding that injury and musculoskeletal ailments were also most prevalent suggests that minor trauma is common in the HAART era among HIV-positive patients as it was in the pre-HAART era [11].

This study found that endocrine/metabolic, psychiatric, infectious/parasitic, and circulatory disorders are most prevalent among hospital discharge diagnoses in this cohort of HIV-infected adults. The finding that psychiatric and circulatory disorders in the inpatient setting have become more prevalent in the HAART era supports previous research that has addressed the nature of inpatient diagnoses in the HIV-infected population [5, 7]. However, the finding of high prevalence of infectious/parasitic disorders in the inpatient setting does differ from some of the most recent studies on the subject. Pulivrenti et al. found that admissions for late-stage AIDS-defining illnesses such as *Cryptosporidium* and *Mycobacterium*

*avium* have declined in their single-center analysis [5]. Our investigation, by using the ICD-9 Diseases/Injuries Tabular Index, more comprehensively analyzed the nature of all hospital discharge diagnoses. While treatment of thrush, for example, may not have been the primary reason for inpatient care, the fact that such treatment was required during the inpatient stay suggests that conditions relating to poor immune function remain an important diagnostic consideration for emergency physicians. The spectrum of illness in the HIV-infected patient population that requires emergency care and hospitalization has grown from just classic AIDS-defining illnesses to other major systemic diseases, such as cardiovascular, neurologic, and orthopedic ailments [12]. Our study confirms that emergency physicians seeing HIV-infected patients must consider both noninfectious and infectious diagnoses in their assessment, even if noninfectious illnesses have become more common.

Future studies on the subject of ED utilization by HIV-infected adults should be conducted in a multicenter fashion to allow capture of patients both in high and low prevalence settings. A larger sample size would also allow analysis of what specific variables are associated with hospitalization, as opposed to ED utilization, which this study was not powered to do. In addition, a prospective methodology will allow a more focused analysis on what are the specific primary ED and hospital discharge diagnoses that require the most health care resources in the HAART era and what factors are associated with their occurrence. However, such a study would require separation of investigators from treating physicians to prevent a Hawthorne effect by increased scrutiny and follow-up care in the outpatient setting than what might normally occur.

## Conclusion

In this study of HIV-positive adults in the HAART era, income level and mean viral load during the study period had a significant association with ED utilization. Noninfectious diagnoses were alone most prevalent in ED discharged, but not hospitalized, patients.

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**Conflict of interest** The authors declare that they have no conflict of interest or disclosures.

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# Management of Uncontrolled Hypertension in a Nurse-Led Clinic Compared With Conventional Care for Patients with Type 2 Diabetes

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**OBJECTIVE** — To compare the effectiveness of a nurse-led hypertension clinic with conventional community care in general practice in the management of uncontrolled hypertension in patients with type 2 diabetes.

**RESEARCH DESIGN AND METHODS** — We studied 120 men and women outpatient attendees (61% non-Caucasian) with type 2 diabetes and a seated blood pressure (BP)  $\geq 140/80$  mmHg. All patients were being treated for hypertension, and 71% had increased urinary albumin excretion (UAE). Patients were allocated to either a nurse-led hypertension clinic or conventional primary care. The primary outcome measure was a change in systolic BP. Secondary outcome measures were total cholesterol, HDL cholesterol, total triglycerides, HbA<sub>1c</sub>, UAE, serum creatinine, and changes in absolute stroke and coronary heart disease (CHD) risk scores.

**RESULTS** — The mean (95% CI) difference in the decrement of systolic BP was 12.6 mmHg (5.9–19.3) ( $P = 0.000$ ) in favor of the nurse-led group, whose patients were three times more likely to reach target systolic BP  $< 140$  mmHg compared with conventional care ( $P = 0.003$ ). A significant fall in 10-year CHD ( $P = 0.004$ ) and stroke risk ( $P = 0.000$ ) scores occurred only in the nurse-led group. There were no significant differences in the reduction of diastolic BP or any of the other secondary outcome measures at 6 months.

**CONCLUSIONS** — Compared with conventional care, a nurse-led hypertension clinic is a more effective intervention for patients with type 2 diabetes and uncontrolled hypertension. A target systolic BP  $< 140$  mmHg is more readily achieved and may be associated with significant reductions in 10-year cardiovascular disease risk scores.

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Hypertension is a major and modifiable risk factor for cardiovascular disease that frequently coexists with diabetes (1). A progressive rise in blood pressure (BP) is also a promoter of renal dysfunction and the development of end-stage renal failure (2). The presence of proteinuria and hypertension also in-

creases the risk of premature death from cardiovascular disease eightfold compared with unaffected patients (3,4). A large evidence base of randomized controlled trials have demonstrated that treating hypertension reduces morbidity and mortality from hypertension-related diseases (5,6). More recently, the use of

antihypertensive agents that interrupt the renin-angiotensin system has been shown to be an effective strategy to retard the progression of nephropathy and reduce cardiovascular events in people with diabetes (7–9). Throughout the western world, expert committees on hypertension recommend that treatment to lower BP is warranted in patients with diabetes who have a systolic BP  $\geq 140$  mmHg (10,11). Currently, hypertension is poorly managed. The Health of England Survey (12) suggests that  $< 30\%$  of affected patients receiving treatment have attained target BP. Furthermore, it has been suggested that with current models of care, the attainment of these stringent BP targets for patients with diabetes may not be attainable in the majority of cases (13). These observations imply that alternatives to conventional care for patients with hypertension and diabetes are required.

Nurse-led clinics (NLCs) can improve care outcomes in some chronic circulatory diseases (14,15). It is unknown whether the intensification of BP management by this approach is more effective than conventional care. Therefore, we studied the effect of a hypertension NLC versus conventional care on lowering BP in diabetic patients with uncontrolled hypertension at high risk of cardiovascular disease. Moreover, we determined what effect this intervention had on absolute coronary heart disease (CHD) and stroke risk scores.

## RESEARCH DESIGN AND METHODS

The study was organized from Whittington Hospital, which serves an inner-city community of 154,000 adults in North Islington, London. Adult patients with type 2 diabetes and uncontrolled hypertension (BP  $> 140/80$  mmHg) were referred to the outpatient NLC from the hospital diabetes clinic. Between June 2000 and June 2001, investigators referred 120 patients.

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Abbreviations: BP, blood pressure; CHD, coronary heart disease; CPC, conventional primary care; NLC, nurse-led clinic; UAE, urinary albumin excretion; UAER, UAE rate.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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All patients previously diagnosed as hypertensive and in receipt of BP-lowering treatment, without any serious or life-threatening comorbid conditions requiring intensive management, were eligible for the study. Patients were considered to have renal complications if they had a history of a persistently elevated urinary albumin excretion rate (UAER) ( $>30$  mg/day) and/or elevated serum creatinine. A BP target  $<140/80$  mmHg was set for patients without renal complications and  $<120/70$  mmHg for patients with renal complications.

### Treatment allocation

Each of the three investigators independently assessed and randomly referred eligible patients from their clinics. Patients were then allocated to conventional primary care (CPC) or the nurse-led hypertension clinic group on an alternate basis. This scheme prevented individual physicians from predicting the treatment patients would receive, thereby eliminating referral bias and generating equally sized groups.

### Baseline clinical and biochemical measurements

At the first (baseline) visit to the hypertension nurse, principal diagnoses were listed along with allergies, current treatment, smoking history, and weekly alcohol consumption. Recreational exercise was graded as low (on feet for less than half a day), medium (on feet for most of the day or regular exercise), or high (regular vigorous exercise). Anthropometric measurements and demographic data (age, duration of diabetes, sex, and racial origin) were also collected.

BP was measured using a validated oscillometric digital monitor (OMRON 705HEM CP; OMRON Healthcare, West Sussex, U.K.) according to British Hypertension Society guidelines. Patients were rested (seated for 5 min). BP was measured in both arms; if no significant difference was found, the left arm was used in future measurements. Measurements were carried out twice with a 2-min rest between each. The second reading was recorded and used for treatment decisions. Absolute 10-year CHD and stroke risk scores were calculated according to the Framingham equation (16).

A 24-h urine collection was made for the measurement of UAER by immunoturbidimetry. In a subset of patients in the

NLC ( $n = 47$ ) and CPC ( $n = 29$ ) groups urinary sodium excretion was also determined. Fasting serum total cholesterol, HDL cholesterol, and total triglyceride concentrations were determined by enzymatic methods. Serum creatinine was analyzed by a rate-reaction method. HbA<sub>1c</sub> was measured by high-pressure liquid chromatography (HA 8121 Biomen; Berkshire, U.K.).

### Follow-up protocol

Patients in the NLC group were seen monthly for 3 months and then every 6 weeks for 3 months. At each visit BP was measured and compliance with the recommended antihypertensive drug regimens was reviewed. These recommendations were guidelines of pharmacological and nonpharmacological management of hypertension, agreed upon by primary care and hospital-based physicians and were in line with those of the National Institutes of Clinical Excellence in the U.K. (10). These guidelines were presented and disseminated to all physicians in the district before the study commenced. A treatment algorithm was not used.

The hypertension nurse emphasized the need for tight BP control, gave nonpharmacological advice for healthy living, and (if necessary) discussed problems regarding side effects of existing antihypertensive treatment. Comorbid conditions were not addressed. The nurse also initiated treatment changes, and new prescriptions were provided by attending physicians. A treatment change was recorded as having occurred if existing drugs were titrated or if a new drug was added on at least one occasion.

A letter stating the measured BP, target BP, and recommendations for treatment according to the common guidelines were sent to the practitioners of patients in the CPC group. At the end of the 6-month follow-up period, patients in the NLC and CPC groups were reviewed by the nurse, and the baseline clinical and biochemical measurements were repeated. The study was approved by the ethics committee of Whittington Hospital.

### Statistics

Continuous data were analyzed with parametric or nonparametric tests according to their distribution and categorical data with  $\chi^2$  test using SPSS version 10.1 for Windows (Chicago, IL). Skewed

data were log transformed before analyses. Multivariable analyses were carried out with the primary end point, with absolute BP or change in BP after follow-up as the dependent variable. For our predefined hypothesis, we calculated that in order to demonstrate a difference of 10 mmHg in systolic BP between the NLC and CPC groups with 80% power at a significance level of  $P < 0.05$ , a total of 60 patients needed to be studied in each group. Analysis was on an intention-to-treat basis. Data are presented as means  $\pm$  SD unless otherwise stated.

**RESULTS** — The baseline clinical data showed that both groups were well matched (Table 1). Antihypertensive treatment regimens consisted of combinations of either ACE inhibitors, angiotensin II receptor blockers,  $\beta$ -blockers, calcium channel blockers, thiazide diuretics,  $\alpha$ -blockers, or the centrally acting agents methyl dopa and moxonidine. Regimens were composed of a median of two agents per patient and based on agents that interrupted the renin-angiotensin system in  $>80\%$  of each group. The proportion of patients in the NLC and CPC groups using ACE inhibitors (61.7 vs. 55.0;  $P = 0.41$ ) or angiotensin II receptor blocking agents (21.7 vs. 30.7%;  $P = 0.58$ ) was similar.

The study was completed by 56 (93%) and 59 (98%) patients in the CPC and NLC groups, respectively. Three patients failed to attend the final visit, and one patient died in the CPC group. One patient from the NLC group refused to continue in the study. After 6 months of follow-up, the proportion of the NLC cohort in which a treatment change took place was higher (88 vs. 15%;  $P = 0.000$ ) and reflected the significant changes in the proportion who received new prescriptions for calcium channel blockers (20.3 vs. 5.4%;  $P = 0.01$ ) and thiazide diuretics (30.5 vs. 3.6%;  $P = 0.000$ ), and the median number of agents per patient, which increased to three, compared with the CPC group remained unchanged from baseline at two ( $P = 0.016$ ).

Systolic and diastolic BP fell within both groups after 6 months. The magnitude of the fall in diastolic BP was similar, but that of systolic BP was significantly greater in the NLC than in the CPC group (Fig. 1). Final systolic BP was significantly higher but diastolic BPs were similar in the CPC and NLC groups (151.0 [21.9]

Table 1—Baseline demographic and clinical data of patients with type 2 diabetes and uncontrolled hypertension allocated to CPC or NLC

	CPC	NLC	P
n	60	60	
Sex (m:f)	42:18	34:26	0.13
Age (years)	62.4 ± 9.1	58.1 ± 13.8	0.95
Diabetes duration (years)	14.2 ± 8.6	14.6 ± 7.5	0.78
Race			0.43
Caucasian	21	26	
Indo-Asian	10	8	
African-Caribbean	27	26	
Far-East Asian	2	0	
Renal complications			0.16
No	14	21	
Yes	46	39	
Smoking history			0.56
Yes	8	11	
No	44	44	
Ex	8	5	
Alcohol			0.70
None	32	33	
Moderate	24	25	
High	4	2	
Exercise			0.86
Low	21	21	
Medium	26	32	
High	7	7	
BMI (kg/m <sup>2</sup> )	29.0 ± 6.4	31.2 ± 6.0	0.06
Systolic BP (mmHg)	157.6 ± 22.8	160.7 ± 23.0	0.46
Diastolic BP (mmHg)	86.9 ± 11.6	87.7 ± 9.8	0.70
Pulse pressure (mmHg)	70.7 ± 20.0	73.1 ± 20.4	0.53
10-year CHD risk (%)	15.1 ± 7.6	18.8 ± 9.5	0.08
10-year stroke risk (%)	9.7 ± 7.4	11.5 ± 8.2	0.24

Data are means ± SD and n.

vs. 141.1 [19.3] mmHg,  $P = 0.02$ , and 82.2 [12.4] vs. 79.9 [10.6] mmHg,  $P = 0.28$ ). Target systolic and diastolic BP were achieved in 38% ( $n = 20$ ) vs. 12% ( $n = 6$ ) and 50% ( $n = 30$ ) vs. 36% ( $n = 22$ ) of the NLC compared with the CPC group after 6 months ( $P = 0.003$  and  $P = 0.26$ , respectively).

There were no changes in the CHD and stroke risk scores in the CPC group. However, there were significant falls in both scores in the NLC group after 6 months (Fig. 2). There were no changes from baseline values in any of the biochemical secondary outcome measures at 6 months in either group (Table 2). Multivariable analysis was performed with the change in systolic BP from baseline as the dependent variable and age, sex, racial group, duration of diabetes, baseline HbA<sub>1c</sub>, baseline systolic BP, baseline total cholesterol, smoking history, alcohol in-

take, and group (NLC or CPC) allocation as independent variables. In the final model, all of the variables were excluded apart from baseline systolic BP and group allocation (Table 3).

**CONCLUSIONS**— We have shown that a nurse-led approach to the management of uncontrolled hypertension in patients with type 2 diabetes is highly effective. Achievement of target systolic BP was more than threefold greater than conventional care. In addition, within 6 months of this intervention there was a significant lowering of 10-year CHD and stroke risk.

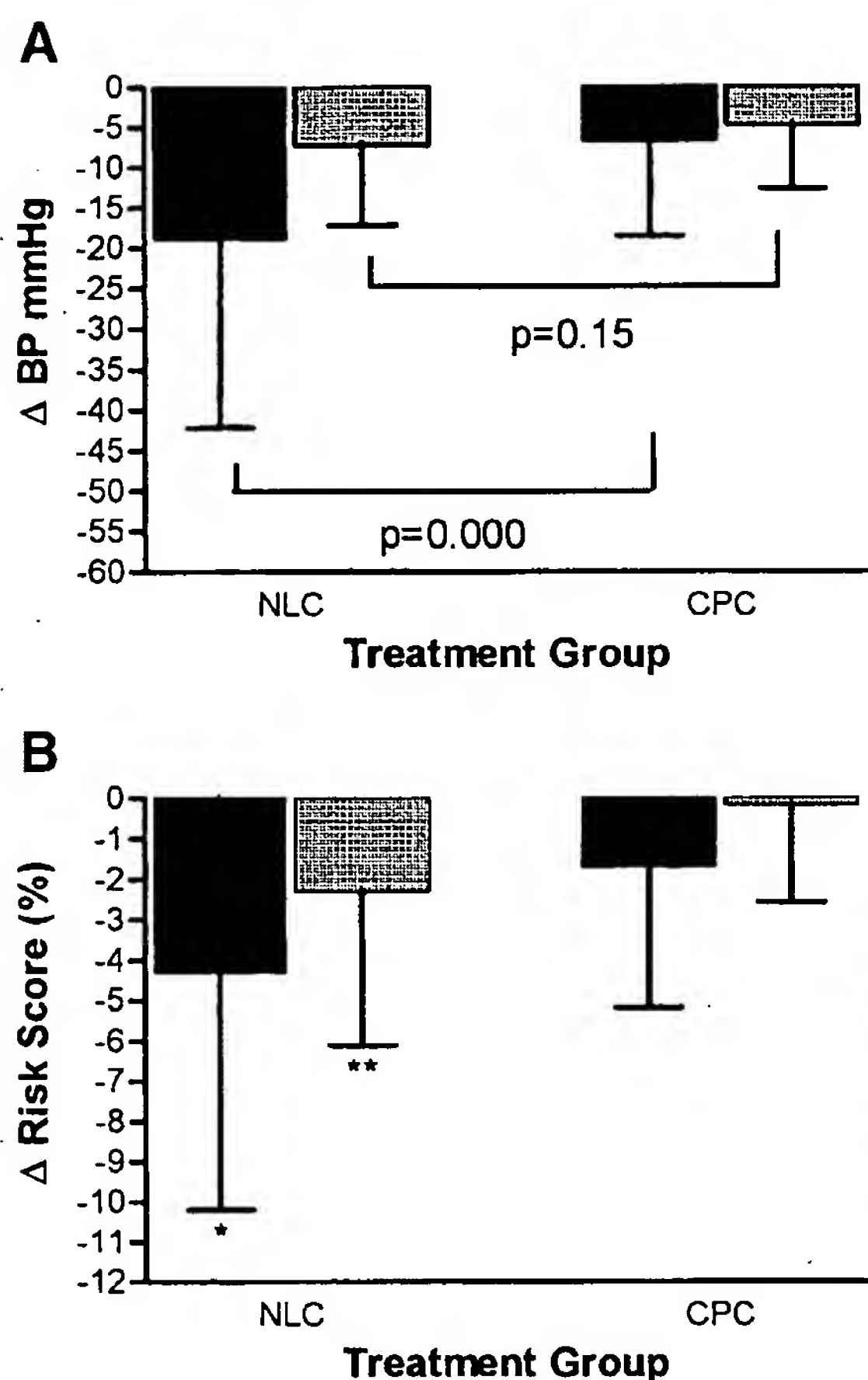
Both groups in this study were well matched at baseline. There were no differences in any of the variables that might be related to the sustained elevation of BP. We did not find any differences in changes in lifestyle measures or surrogate

markers of dietary changes (sodium excretion and body weight) that might have contributed to these results. Moreover, none of the biochemical secondary outcome measures were altered by the intervention. This intervention focused on intensifying antihypertensive treatment. The hypertension nurses and the primary care physicians used the same guidelines, which were based on the evidence used and recommended by the National Institutes of Clinical Excellence in the U.K. (10). The majority of patients were already in receipt of agents that interrupt the renin-angiotensin system, which are considered first-line treatment of increased albuminuria that coexists with hypertension (17). The treatment changes mainly involved adding thiazide diuretics and calcium channel blockers, which are efficacious in combination with ACE inhibitors in lowering BP (18,19).

A challenge for health care providers is translating research findings into clinical practice. Patients in research settings on several drugs for hypertension can achieve high compliance, effective BP lowering, and low drop-out rates during the life of the studies (18,19). In our study, one of the patients in the NLC group was lost to follow-up, whereas 5% of the CPC group failed to attend the 6-month visit. Reanalysis of the data with only the patients who completed the study had no effect on the size of the differences in the primary outcome measures (data not shown).

The focus on hypertension and its management by the hypertension nurse provides much of the organizational similarities in research settings. Organizational factors are considered by some to be more important than guidelines in contributing to poor levels of BP control in patients with diabetes (20). Lowering BP in hypertensive patients and improving the quality of life of patients with heart failure has been shown to be more effective in community NLCs than in hospital-based services (14,15,21). Together, these data support our observations that a nurse-led approach per se is an effective strategy in the intensification of BP management for patients with type 2 diabetes.

The reinforcement of patient education positively affects BP control and possibly contributed to our findings (22). However, we did not formally assess patient education. Neither can we exclude an improvement in compliance with



**Figure 1**—A: Mean (95% CI) fall in systolic (■) and diastolic BP (▨) in patients allocated to CPC and NLC after 6 months of follow-up. B: Mean (95% CI) fall in 10-year stroke risk (■) and CHD risk (▨) in patients allocated to CPC and NLC after 6 months of follow-up. Differences in stroke\* and CHD\*\* risk from baseline were significant at  $P = 0.0000$  and  $0.004$ , respectively.

**Table 3**—Stepwise multivariable analysis with change in systolic BP after 6 months as the dependent variable

	$\beta$	$t$	$P$
Baseline systolic BP	0.585	6.381	0.000
Treatment allocation group	0.248	2.880	0.000

more likely to have their treatment regimen adjusted compared with those in conventional care. Therefore, we consider rigorous application of the guidelines in the context of nurse-led management to be the key to greater improvement.

The majority of our patients were at high risk of premature death due to cardiovascular disease in the presence of increased albuminuria. Tight BP control has been recommended for patients with type 2 diabetes and renal involvement. A target of  $<135/75$  mmHg is recommended by the National Institutes of Clinical Excellence (17). Moreover, data from the Modification of Diet in Renal Disease Study Group suggest an even lower target BP of  $<120/70$  mmHg to limit progressive renal disease (25). In our study, the level of albuminuria was unaffected by BP lowering. This is consistent with studies showing low rates of resolution of microalbuminuria and suggests that strategies in addition to BP lowering are required to prevent the progression of nephropathy (8).

Our findings are relevant to the delivery of care in relation to the National Service Framework requirements for diabetes and cardiovascular disease in the U.K. Our model may be generally applicable and enhanced if algorithms are developed for nurse specialist/practitioners

treatment as a factor in the improved outcome. In a recent report (23) of patients with resistant hypertension, a lack of compliance with medication was not shown to be the cause of failure to reach target BP. Improved access to monitoring and pharmacological intervention facilitated by the hypertension nurse appears to be central to the outcome of this study. The greater reduction in BP in the patients allocated to nurse-led care was related to

the greater frequency of changes in treatment. The guidelines were effective as BP was significantly lowered in both the conventional and nurse-led groups. Our observations are consistent with a previous study (24) that suggests that failure to change treatment, despite frequent monitoring of BP, is an important factor in the poor management of hypertension in specialist clinics (24). The patients in the nurse-led groups were nearly six times

**Table 2**—Biochemical data at baseline and at 6-month follow-up for patients with type 2 diabetes and uncontrolled hypertension managed in a NLC and in CPC

	NLC		CPC	
	Baseline	6 months	Baseline	6 months
Total cholesterol (mmol/l)	4.9 (1.0)	4.8 (0.9)	4.8 (1.0)	4.7 (0.8)
HDL cholesterol (mmol/l)	1.4 (0.4)	1.3 (0.3)*	1.4 (0.4)	1.4 (0.5)
Triglycerides (mmol/l)	2.5 (1.9)	2.4 (1.7)	2.5 (2.6)	2.3 (1.4)
HbA <sub>1c</sub> (%)	8.2 (1.8)	8.2 (1.4)	7.9 (1.7)	7.9 (1.9)
UAE (mg/24 h)	33.0 (14.3–136.3)	39.2 (16.0–200.0)	55.0 (18.4–151.4)	30.5 (14.5–147.2)
Urine sodium (mmol/day)	182.5 (67.7)	178.7 (103.1)	172.8 (88.1)	177.3 (87.7)
Serum creatinine ( $\mu$ mol/l)	113.4 (39.5)	117.6 (40.2)	120.2 (38.8)	114.7 (37.2)

Data are median (interquartile range) for UAE values. \*HDL cholesterol lower at 6 months,  $P = 0.02$ .

with appropriate prescribing authority. Tight control of BP for patients with newly diagnosed type 2 diabetes is cost effective (26). The cost-benefit of our approach for patients at higher risk of cardiovascular disease needs to be explored and the sustainability of the effect confirmed. Further, longer-term studies using this approach for specialist care for patients with diabetes are now required.

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